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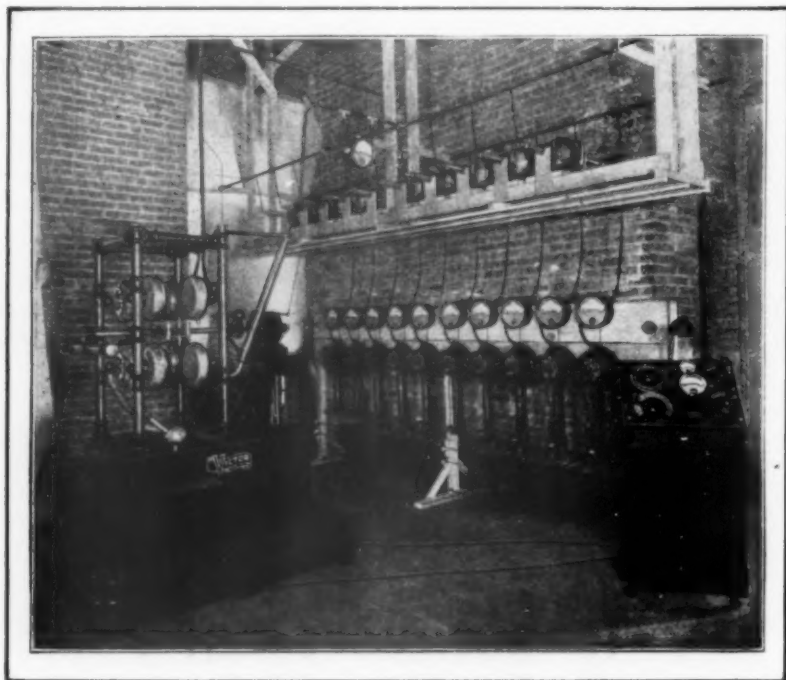
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VOL. IV

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Twentieth Century Advances in Cancer Research*

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INTRODUCTION

I have thought that a survey of cancer research at this time, albeit incomplete and more or less popular, might be of interest, because the subject is highly technical and requires for its mastery more time than the ordinary physician or educated layman has at his disposal; because it takes a considerable time for the newer researches to become a part of current knowledge, and finally, because only a specialist can decide what is important and what is trivial, mere speculation, or theory without an adequate experimental basis, and he not always.

The most striking difference between the researches of the last twenty years and earlier researches on cancer is that while formerly the chief dependence was placed on *observation*, latterly the open sesame of exact *experiment* has been added, and that too on a large scale, in many localities. Paraphrasing Borrel, we may now say: twenty years of experimentation have taught us more about cancer than the previous twenty centuries of sterile observation.

In what follows I shall touch only on the conspicuous features of a few of the outstanding experimental researches of the last twenty years, and it must be understood that many of these experiments were suggested by earlier observations and cruder experiments, which for lack of time and space I shall not mention, but which nevertheless would have their place in any full historical survey. Such a full survey has been attempted by Jacob Wolff and covers more than 2100 closely printed octavo pages (Gustav Fischer, Jena, 1907, 1911) and would require at least another 500 pages to bring the subject up to date.

In 1896 the German cancer pathologist, Dr. Hugo Ribbert, a strong personality, energetic, persuasive in

speech and facile with pen and pencil, propounded a doctrine of cancer causation which within the next ten years overturned pretty much everything that had been received during the previous half century as certain or probable in cancer research, beliefs founded on the labors of many men, and conspicuously in Germany on those of Thiersch, Waldeyer and Virchow, three very great names in human anatomy and pathology. These men held an open mind as regards parasitism in cancer but Ribbert's mind was closed and sealed to all such explanations.

By 1905, partly through Ribbert's writings, partly as a result of the failure of many attempts at isolations, the idea of parasitism was so entirely set aside that no European cancer worker of any great importance believed in it any more, not even Ribbert's opponents.

Cohnheim's theory of embryonic "rests," which for a time displaced Virchow's irritation theory, having now been abandoned as contrary to a multitude of clinical observations, Ribbert advanced the idea that cancers are due to the multiplication of one or more epithelial cells displaced from their fellows by trauma or by excessive connective tissue proliferation, which he conceived to be always the necessary first stage in the cancerous process. Hauser, Hansemann and other opponents, while agreeing that no parasite is involved, strenuously maintained that the first tissue to proliferate is always the epithelium and that connective tissue proliferations are always secondary, non-essential and sometimes altogether wanting; and that view continues to be the general opinion today. Ribbert first maintained that all the morbid proliferations of a cancer are the product of a single cell or cell-group but later he was forced to qualify this view and to accept the doctrine of multicentric origins for such cancers as were described by Krompecher and by Petersen, but always he strenuously denied that there could be any conversion of adjacent normal cells into cancer cells, although

it is not a far cry from multicentric origins to growth by apposition, as Lubarsch has pointed out.

Ribbert's explanations were largely theoretical, based on assumptions, and may be said to have raised more questions than they settled, and more and more in recent years his theory even when modified so as to be scarcely recognizable is seen to be inadequate. The modern drift is entirely away from Ribbert's ideas.

At the present time a considerable number of cancer workers have come to believe that, after all, cancers may be due to parasites or viruses, while the greater number perhaps, occupy a middle ground, neither believing nor disbelieving but awaiting evidence, and only a minority still strenuously maintain the non-parasitic view. Most workers are convinced, however, that if not always, at least nearly always, cancers begin in continually irritated places. The amount of clinical evidence in favor of such a belief is enormous, the experimental evidence obtained on the lower animals is incontrovertible and accumulating all the time and the practical leadings of such a view are obvious. We will now take up some of the observations and experimental researches which have led to this change of opinion, and which seem to point to parasites as probable causes.

I. TRANSPLANTATION EXPERIMENTS

We may first consider a few of the results obtained from transplantation experiments.

Beginning with Jensen's brilliant work on mouse cancer, in 1901-03, workers in many laboratories took up and diligently followed this lead, using at first his mouse cancer and subsequently many other forms of cancer found in mice and rats and other experimental animals, and to such an extent that some cancer laboratories have had as many as 20,000 mice under observation at one time and often as many as several thousand. Jensen was not the first to successfully transplant

*(With special reference to etiology.)
Read at the Annual Meeting of the Radiological Society of North America, Detroit, Dec. 7, 1922.

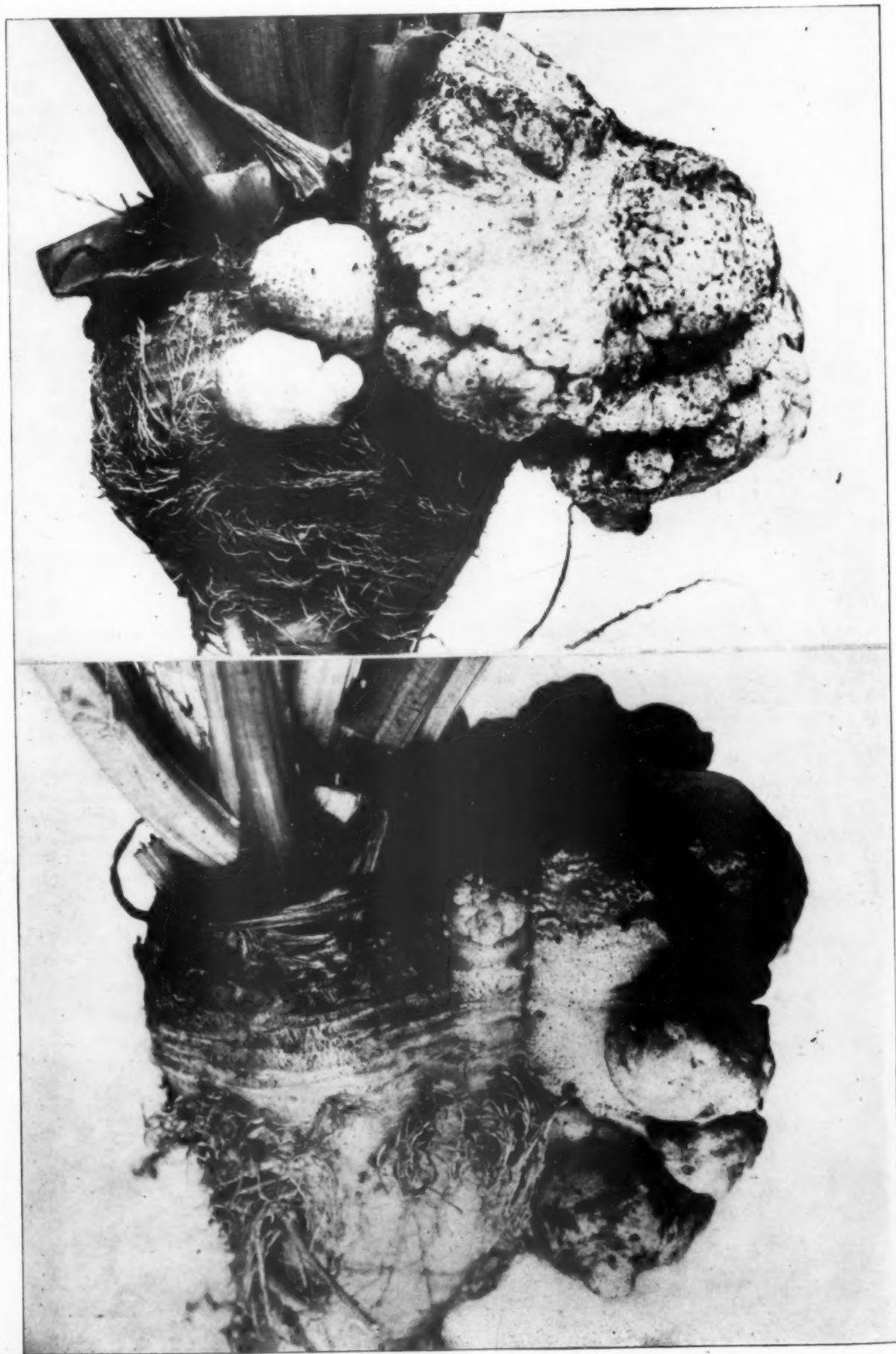


Fig. 1—Sugar beets inoculated two months (Spring of 1923) by needle pricks, using hop strain of *Bacterium tumefaciens* through sunflower (Colony 1) and showing simple conjunctive tissue tumors. About natural size. Necrosis (dark speckling)

has begun. To kill the plants inoculations should have been made earlier and centrally. See Plates 2, 3, 4 and J. Cancer Research, 1:No. 2, Plates VII and VII-A.

cancer. Leo Loeb's work on rat thyroid sarcoma was earlier and there were others before him, but Jensen's work arrived at the psychological moment, which always means a great deal, and he was able and willing to give his tumor to all who asked for it.

These transplantation or grafting experiments have taught us many things as to the behavior of cancer under a great variety of controlled conditions, and may teach us much more, especially as to therapy, but nothing definite has been learned from them as to etiology unless it be this that a cancer may begin as a carcinoma and end as a sarcoma. The transplants are to be regarded as artificially produced secondary tumors and a study of their behavior tells us nothing about how the parent cells became abnormal.

One striking result has been the discovery that, in general, animal cancer is transplantable only within very narrow limits, viz., within the species in which it has originated, and often within still narrower limits such as particular races of a species or individuals of a race. Growth nearly always follows when a fragment of a spontaneous tumor is re-introduced into the same animal in which the tumor has arisen, whereas the result is positive only in a very small percentage of other spontaneously attacked and normal mice (Haaland, 1911). This proves nothing, however, as to what cultures of a cancer organism might do in susceptible races when introduced in quantity so as to obtain "mass-action," and quite recently we have come to believe that this feature of transplantation has been overstressed and that under certain conditions cancers are more widely inoculable by transplantation than was formerly supposed. Rous showed that his chicken sarcoma No. 1, transplantable and inoculable at first only within one family of a race, could later be produced in other families of this race and finally in other races of the species. Sticker claimed that when he transplanted a dog cancer into a fox the tumor continued but only fox-cells grew. Dagonet maintained that he transplanted lymph-gland metastases of a recurrent human penis carcinoma into the abdomen of a rat with positive results in the spleen and liver where a structurally identical keratinizing carcinoma developed. Here, of course, it was not the human cells that grew. Carl Lewin states that he obtained positive results in the abdomen of a dog by transplanting a rapidly growing very malignant human ovarian carcinoma, but the resulting tumor in the dog was a round cell sarcoma which he subsequently carried through five transplant generations. Several other workers have claimed similar positive results but all

of these have been on too small a scale to preclude accident or else the resultant tumors have been interpreted by other cancer workers as granulomata.

Keysser, the last, who has had much experience with Wassermann, and who is privatdocent for surgery in Jena, says that all his earlier efforts to transplant tumors from one animal species to another were negative, corresponding to those of Uhlenhuth, Weidanz and Sticker. He finally succeeded, however, he says, by what he calls *increasing the sensitiveness and decreasing the specificity* of the tumor to be used as a transplant. For his first experiment he selected a very virulent, recurrent testicle sarcoma, the large metastases of which on the breast and abdomen had at first receded under x-ray but had returned four weeks later and were then resistant to and irritated by x-ray. The virulence of this tumor was further heightened by giving the man an autolysat injection of a shoulder sarcoma from another man. Following this injection the growth of the subcutaneous metastases increased rapidly and after five weeks the metastases were extirpated and a fine water-emulsion prepared which was injected into various organs of mice. One mouse died at the end of 9 months with a cherry-stone size, solid, white sarcomatous tumor in the liver, pinhead nodules in the spleen, and 3 c. c. of blood in the abdominal cavity. This liver sarcoma has been transplanted through four generations (Arch. f. klin. Chir., 22 Okt. 1920, S. 730-736) with increasing virulence but the growth progressed much more slowly than in transplants of tumors from mouse to mouse. Here it would seem, since human cells are not likely to have grown in a mouse, that, if what happened stands in any relation to what was done, a cancer virus was transmitted, and, in the light of Rous's work on chicken sarcoma, this is not improbable. But one swallow does not make a summer.

Transplantation experiments have shown also that the host provides the stroma, that generally, at least, it is only the inserted tumor cells which grow and but a small part of these yet possibly there are exceptions (Borrel, Sticker, Lewin, et al); and that resistance to cancer is an extremely variable matter within the individuals of a given race and even within the same individual at different times.

Another striking thing, now well demonstrated by many observers is that a transplanted carcinoma may grow for a series of generations in its original form and then become a mixed carcinosarcoma and finally a pure sarcoma (vide Leo Loeb, 1903, and Bashford, Imp. Cancer Res. Fund, 4th Sci. Rep., 1911). This change from an epithel-

ial to a connective tissue tumor has been explained in various ways, all hypothetical, as for example: (1) the carcinoma in some way chemically stimulates the connective tissue, either its own or that of the host, it is not certain which, into a sarcomatous growth; (2) the carcinoma has transmitted some cancer germ or virus to the neighboring connective tissue cells; (3) the spindle shaped cells are changed epithelial cells, i. e., the tumor is really a carcinoma masquerading as a sarcoma (Krompecher's view).

It was believed for a long time that mouse cancer transplants never produced metastases, and ordinarily they do not when placed under the skin, but they may do so as a result of traumatism or if placed in deeper parts of the body.

Multicentric origins are frequent in mammary tumors of the mouse (Haaland).

II. RESEMBLANCES OF CROWN GALL TO CANCER

In 1907, and many times since, the writer and his colleagues in the United States Department of Agriculture (Brown, Townsend and McCulloch) showed that a widely distributed plant tumor, known as crown gall, is due to a schizomycete (*Bacterium tumefaciens* Smith and Townsend), and with virulent strains of this organism can be produced at will (100 times out of 100) on sensitive plants by pure-culture inoculations.

Also beginning in 1909 the writer pointed out repeatedly, and is still doing so, many ways in which this tumor seemed to him to resemble malignant animal tumors. The following are some of these ways:

Existence of primary tumors giving rise to tumor strands on which are secondary tumors having the structure of the mother tumor, which tumor may be a plain connective tissue hyperplasia or a solid embryoma; tumors non-capsulate growing chiefly from the periphery and composed of innumerable, disoriented, rapidly-multiplying, easily-perishable, deep-staining, invasive or crushing, single-nucleate or multinucleate tumor-cells, supported by a variable amount of stroma consisting of cortex cells or their equivalent (ray cells and pith cells) and of distorted vessels developed out of the round-about normal tissues; growth by apposition occurs and the nuclei, which usually divide by mitosis, are often notched and cleft or even completely divided without mitosis. How long the tumor remains alive depends apparently on the amount of its stroma.

As the tumor grows, neighboring tissues are crushed and exfoliated, distal tissues are starved while proximal tissues especially those under or in the



Fig. 2—Crown-gall inoculations on *Bryophyllum calycinum*, showing dwarfing and killing effect of inoculating young plants in the terminal bud region. Of the ten plants in the foreground all are dead except the two at the left (time, nine months). Controls in the background. These plants were exhibited May 1, 1922, at the Washington meeting of the Ameri-

can Association for Cancer Research, at which time all were alive and the controls much smaller. They were inoculated by needle pricks with *Bacterium tumefaciens* plated from a tumor on the peach. Behind the screen are the controls of the plants shown in Figure 3. Photo, Sept. 8, 1922.

vicinity of the tumor are often swollen by excessive multiplication of normal cells, i. e., a collateral hyperplasia is developed. The tumors may be cut out or destroyed by caustics but are liable to return; they decay first centrally. The growth is injurious to the whole plant if it is centrally located, i. e., not on some remote root or branch. Apparently some species are immune (olive, onion, garlic), others are slightly susceptible (avocado, most monocotyledons) and still others highly susceptible (raspberry, blackberry, rose, peach, almond, grape). There appears to be also a variable individual resistance within the species or variety. In susceptible species the amount of injury depends greatly on the age of the plant and on the location of the tumor. One successful crown-gall inoculation does not protect the plant from a second infection. Young plants are most susceptible and may be killed by a terminal bud inoculation and when not killed are badly dwarfed.¹ The organism probably gets in only through wounds and probably lives in the soil. In one instance I observed development of the tumor two years after the inoculation. These facts are so well known that I need not here do more than recapitulate. I will only stop further to say that they came from such a strange source that they did not make much impression on cancer workers, at least not at first. When I began to write on crown gall and talk to cancer specialists about it they laughed at me. That any cancer could be caused by a parasite was then believed to be impossible. The cell itself was regarded as the only and all-sufficient parasite. Now we know of half a dozen cancers due to parasites, and there will be more when all the experimental evidence is in.

One of my manuscripts was rejected by a German journal as "zu Botanisch"; a second German critic said, "The disease has nothing in common with cancer but its name," while a third likened the tumor to smut balls in maize, which it does not in the least resemble, and said all this had been known in Germany for a long time; but I have lived to see several long papers on crown gall published by German workers in their cancer journal (Zeitschrift f. Krebsforschung) and also the establishment of a special section for the study of plant tumors in the German Imperial Institute for Cancer Research in Berlin. I recall also, very well, certain kindly but sceptical comments which followed the reading of my first paper before the American Association for Cancer Research in 1909. One colloquy was about as follows: "Well, Doctor, you have a very interesting disease but it has nothing to do with

cancer." "Why not?" "But you produce it with a parasite, do you not?"

"Yes." "Well, there is no parasite in cancer!" Here was Ribbert's dictum over again, the whole argument based on an assumption and revolving in a circle, just as in the past we have heard the same argument applied to leprosy and tuberculosis. Gradually, however, I succeeded in interesting a great many physicians and surgeons, at home and abroad, and won over various persons. In America Cullen, Adami, Bloodgood, Weil, Abbe, McCarty, Gaylord, Loeb, Hazen, and other cancer men expressed great interest in my work. In Paris, Borrel of the Pasteur Institute accepted it, and in Copenhagen, Jensen.

Borrel (1912) wrote as follows (1er Cong. Int. Path. Comp. T. I):

"Pour nous, le cancer est une maladie infectieuse et le caractère particulier de cette infection est précisément de créer dans l'organisme par une véritable symbiose une cellule nouvelle, une cellule lichen, un organisme nouveau, le cancer qui est bien au sens des anciens le crabe rongeur attaché à sa proie, l'être monstrueux nouveau capable de se multiplier indéfiniment sur de nouvelles victimes: la cellule cancéreuse doit être considérée comme le produit incestueux d'un parasite et de son hôte.

"Cette symbiose nous la retrouvons surtout dans le règne végétal, (la pathologie n'est pas forcée de s'arrêter au règne animal), elle caractérise les lichens, elle caractérise les nodosités des légumineuses où nous voyons le protoplasma cellulaire comme remplacé par des milliards d'êtres microscopiques qui sont les bactéroïdes; nous la retrouvons dans les tubercules des orchidées et des bégonias où la présence d'un parasite rend vivaces des cellules qui sans cela seraient éphémères. On les a retrouvés, ces parasites, sous forme de mycorrhizes dans les racines de presque tous les végétaux vivaces. * * * * * nous la retrouvons, le fait vient à peine d'être établi, dans les tumeurs cancéreuses végétales si bien étudiées par Smith et qui ont des métastases comme de vrais cancers humains. Le fait est capital, ces tumeurs sont greffables comme les cancers animaux et greffables en tant que cancer, comme Jensen l'avait établi avant que Smith ne découvre le microbe et voilà le premier cas d'un cancer véritable répondant à la définition du cancer et causé par l'inoculation directe d'un microbe; une tumeur de la betterave inoculable à la betterave par greffe et inoculable à la betterave et à beaucoup d'autres végétaux par des cultures.

"Nous n'avons pas encore un cancer animal de démonstration pareille, bien que certains observateurs considèrent le cancer de Sticker comme greffable et inoculable. Nous ne savons pas inoculer le cancer chez les animaux et pour cela le virus reste à l'état d'hypothèse, mais je dirai à l'état d'hypothèse probable. Les expériences de Rous, faites à l'Institut Rockefeller, si la tumeur étudiée chez la poule est bien un sarcome greffable, seraient le premier exemple d'une tumeur cancéreuse inoculable directement et inoculable par un virus filtrant."

In Copenhagen in 1918 Jensen, the well-known student of animal cancer, the discoverer of Jensen's mouse cancer, and the Director of the Serum Laboratory of the Danish Veterinary and Agricultural School, published in Dan-

ish a paper on crown gall embodying his own experiments of the preceding ten years, but also discussing the work done elsewhere, and especially that done in the United States Department of Agriculture. After stating that on critical examination of most comparisons between plant and animal tumors the analogy entirely fails, he continues as follows:

"An exception in this respect is found in a tumor-form met with in many species of plants and known in America under the name of 'crown gall'; through several years has this disease been the object of thorough investigations by Erwin F. Smith and his co-workers. In the last years through these investigations interest has been aroused in wider circles for this plant tumor that has by Erwin F. Smith (and beyond a doubt correctly) been placed as analogous to the malignant neoplasms in animals. (Serum Laboratory No. LIV, p.96).

"The beet-tumors are undoubtedly caused by the already named *Bacterium tumefaciens* but when I commenced my investigations this fact was still unknown, and everything seemed to indicate that this new formation had no origin of this kind. In spite of the bacterial origin of the disease, this new formation in beets (and in several other plants) is of the greatest interest from a comparative oncological point of view. (p. 97).

"As also mentioned, I thought, when I commenced my researches, that I might consider it certain that parasites formerly brought into etiological connection with the tumor-formation could not be made responsible for this; and rather far-reaching investigations, especially bacteriological, which I, myself, undertook did not show any microbes that might be considered the cause of the disease. Hence, I considered it rather certain that the tumors of the beets were not of a parasitic origin. In the meantime in 1911² a thesis was published by Erwin F. Smith and his co-workers, Nellie A. Brown and C. O. Townsend that made it necessary to take up anew the search for microbes in the tumors of the beets. (p. 122).

"Hence, I can fully share the opinion of Erwin F. Smith that 'crown gall' is a new formation which (irrespective of the cause of its formation) can be placed side by side with the real malignant tumor-formation in the higher animals. (p. 136).

"The author draws, and undoubtedly with full right, very far-reaching analogies between the forms examined of 'crown gall' and the malignant tumors of animals. (p. 134).

"Through all these properties this tumor shows very considerable points of similarity with the animal malignant tumors, especially with the carcinomas." (p. 135).

Recently after seeing many of my inoculated plants and stained sections the English pathologist, Dr. E. J. Butler, wrote as follows in his paper on "Some Relations between Vegetable and Human Pathology" published in the London Lancet (Jan. 21, 1922, p. 160):

"The first is tumour formation in plants as exhibited by the well-known crown-gall tumour caused by *Bacterium tumefaciens*. I have recently had an opportunity of discussing with Dr. Erwin F. Smith, of Washington, this disease, which he has been studying for the last eighteen years. His work is regarded by plant pathologists throughout the world as of great value. The tumours caused are usually hyperplasia, arising from the repeated division of the cells to produce a solid small-celled tumour tissue without cavities. The cells are



Fig. 3—Crown-gall inoculations on *Bryophyllum* (time, eleven months). Two dead and the others dwarfs. Controls of same age and origin, and under the same conditions as to light, water, size of pots, etc., are shown in the background. Beyond these are the tobaccos referred to (Figure 4) as inoculated six inches below the terminal bud. These plants were

exhibited May 1, 1922, in Washington at the annual meeting of the American Association for Cancer Research. They were inoculated Sept. 16, 1921, with *Bacterium tumefaciens* from hop by needle pricks in the region of the terminal bud when they were about six inches high, that is, larger than those of the preceding figure. Photo, Sept. 8, 1922.

often markedly embryonic in character and divide mitotically and amitotically. Secondary tumours frequently develop, often at a considerable distance and deep-seated in the tissues. They are not caused by migration of the bacteria across normal tissues, but by a definite outgrowth from the primary tumour in the form of a tumour-strand of infected cells of marked characters and easily recognized in section, though often only a few cells thick. Such strands have been traced for eight inches in length. The secondary tumours have the characters of the primary, so that if a leaf bears tumours secondary to one on the stem their structure will be a stem structure. Secondary tumours can also be produced by grafting a part of a primary tumour on a suitable part of the plant. Growth of the tumour is unlimited and devoid of polarity, and the destructive action on the plant is usually merely the result of pressure and crushing, though necrosis permitting secondary infection is common.

"The structure of the tumour varies according to the tissue primarily infected. Most of them are of the ordinary ground or conjunctive tissue cells—e. g., in the cortex or pith—and are the nearest approach that one could expect to get in plants to sarcomata. There is no epithelium in plants, and the epidermal tissues are thin, usually a single layer, and hard to inoculate without involving the underlying ground tissue. But a few cases have been described in which the tumour appears to be composed mainly of epidermal elements, including hairs (the plant hair being an outgrowth from a single epidermal cell), and these may be compared with epitheliomata. The most interesting type, however, is undoubtedly the embryomata. These tumours, first detected as recently as 1916, are composed of a jumbled mass of young shoots and roots of usually incomplete structure having only bits of organs, but sometimes forming more or less complete dwarf shoots. The secondary tumours developed from these have usually the same embryonic teratoma structure.

"The organism which causes crown gall is a cell parasite of a highly developed type, in which the host cell is not destroyed but is stimulated to increased activity. There are many such cases in plant parasites. To the best of its ability the parasite aims at preserving the life of the host cell for its own needs. That it over-stimulates the cells, causing death by crushing and necrosis, may be regarded more or less as an accident. *Bacterium tumefaciens* can be isolated and cultivated, so that its morphology and characters are well known. It is rare in the tissues, at least in an active state; in one case it was estimated that there were only 200 living bacteria per cubic centimetre of the tumour. But perhaps the most significant thing that I learned from Dr. Smith was that, contrary to his earlier belief, he is not now certain that he has ever recognised the organism in the tissues. What he previously saw he now thinks were only cell-inclusions or chondriomes. Thus we have a parasite capable of causing a tumour having all the characters of a malignant growth; the organism has been isolated, grown in pure culture, and new tumours produced at will with it, but it is not with certainty to be recognized in the tissues of the tumour.

"More recently Dr. Smith has been able to produce experimentally small tumours of limited growth, having the characters of incipient crown galls, by injecting in suitable parts of plants certain of the diffusible products of the metabolism of *Bacterium tumefaciens*, including ammonia, amines, organic acids, etc., and he considers that the tumour is ordinarily caused by the continual production of small quantities of these excreted products by the parasite.

Application to Cancer Research

"I am aware that the path of cancer research is strewn with the wrecks of parasitic theories, but the recent work on plant cancers, the experimental production of embryonic teratomata, the extreme difficulty of detecting the parasite in the cells (it is certainly in, not between the cells³), and the evidence that it acts by the production of repeated small quantities of an excreted stimulus, makes it easy to understand the view held by Dr. Smith and other vegetable pathologists, that cancer will ultimately be found due to some similar cause."

III. ROUS'S FILTERABLE VIRUS CHICKEN SARCOMAS

The first body-blow to the doctrine that the cancer cell is the only parasite came from work done in the Rockefeller Institute for Medical Research in New York by Peyton Rous and his associates (chiefly James Murphy) on chicken sarcomas. They were not able to isolate the agent and determine the cause of the tumors, but experimenting through a series of years they demonstrated indubitably that the filtrate of the crushed tumor cells will cause the disease, and a little later that the virus persists in cells killed by freezing, by heat, by drying, and by glycerin.

Rous's first paper published in 1910 was followed by many others (I have read 25) detailing the results of an enormous amount of exceedingly interesting experimental work. He was the first to demonstrate that an avian tumor is transplantable. This tumor (his sarcoma No. 1) retains its morphology with continued transplantation, increases in virulence, metastasizes and invades. The host rapidly emaciates, becomes cold, weak, somnolent and often dies within four or five weeks from the time of tumor inoculation. As the transplantations continued, the virulence rose, the number of "takes" increased and the metastases became much more frequent. The latter were found in the heart, lungs, liver, kidneys and peritoneum. Most of these metastases are by way of the blood stream, more rarely through the lymphatics. Lung and heart metastases are very common and these organs may be almost completely replaced by tumor tissue. In several cases there was direct extension of the tumor in vessels. The tumor was found in a barred Plymouth Rock fowl and at first the transplantations succeeded only in occasional Plymouth Rocks of the same immediate descent but subsequently other Plymouth Rocks were found to be susceptible and also Brown Leghorn fowls. The tumor was discovered in 1909 and by 1911, Rous was able to produce it by transplantation in 80 to 100 per cent of barred Plymouth Rock fowls and it was especially active in the young. It would not cause tumors in other animals—pigeons, ducks, rats, mice, guinea pigs. The tumor had and still has all the

characteristics of a spindle-cell sarcoma. Cultures from it in various media, were sterile as regards bacteria. Now came the great surprise: the clear fluid obtained from the ground tumor by means of coarse or medium Berkefeld filters impervious to such bacteria as *B. prodigiosus*, and *B. fluorescens liquefaciens* was found to cause the sarcoma when injected. It was also produced by introduction of the tumor cells after being dried, or killed by heat, by glycerin, or by repeated freezing and thawing.

Only a small proportion of the injected fowls develop the growth when the Berkefeld filtrate is used and the tumors are few in number. They occur along the needle track and are much slower in developing than when tumor tissue is used but otherwise they are typical. On the contrary when the irritating tumor powder was introduced in Ringer's solution the tumor was found in many fowls. Powdered diatomaceous earth was then introduced along with the filtrate to increase its infective power and in such cases the tumors were more frequent and were multicentric at first but subsequently coalesced. This earth injected alone does not cause tumors but it is quite plain that the introduction of diatomaceous earth or dried tissue sets up an irritation exceedingly favorable to the production of tumors when the virus is present. This agrees very well with the generally admitted fact that human cancers often, if not always, begin in irritated places.

By 1913 the tumor had been transplanted through 32 series of fowls (a total of 217).

The tumor agent being separable from the tumor cell the old doctrine that "the tumor cell is the only parasite" falls to the ground, so far at least as relates to chicken sarcomas and presumptively to all sarcomas. What this agent may be no one knows. In 1912 Rous spoke of the "causal agent" as "ultra microscopic in some, perhaps in all, of its forms and undoubtedly a living organism" (Proc. Amer. Phil. Soc.). In 1913 Rous and Murphy speak of the agent more caustically as "probably a living organism."

The agent or virus has the following properties: It does not attack epithelium. It is destroyed by tissue autolysis, by 50 per cent alcohol, by 2 per cent phenol, by saponin in high dilutions, and by chloroform and toluol in such quantities as are destructive to bacteria. It is destroyed by temperatures above 53° C., and will endure only a little more heat than the tumor cell. It resists long drying. It stands freezing and thawing well. It withstands 50 per cent glycerin for at least a

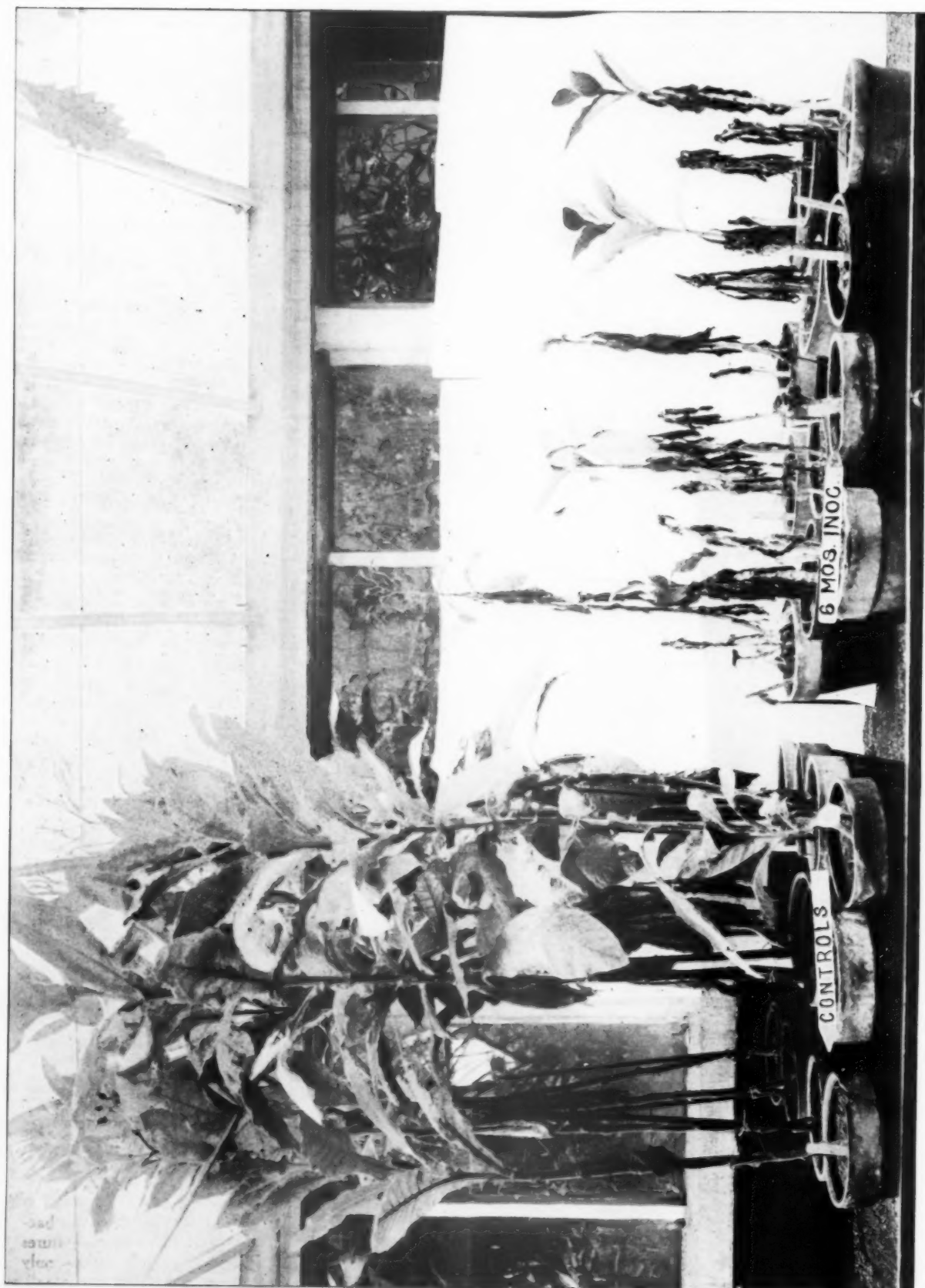


Fig. 4—Effect of inoculating *Bacterium tumefaciens* by needle pricks into the region of the terminal bud in young tobacco plants. The organism used was cultivated from a tumor on the bench. All developed tumors, also the main axis was killed in all. Of the fifteen inoculated plants, eight died, and seven pushed dwarf basal shoots and one fruited sparingly. Three controls are not shown in the photo. All died about two months later. Controls at

the left. These plants were exhibited May 1, 1922, in Washington at the annual meeting of the American Association for Cancer Research, at which time all were alive. Of another set inoculated at the same time and in the same way (by needle pricks) but six inches below the terminal bud, that is, in a less critical region, all developed tumors and all were somewhat dwarfed, but all blossomed and fruited. (See left side of figure 5, A, B, C Photo, Sept. 8, 1922)

month. It will not pass a porcelain (Chamberland) filter or a dialyzing membrane. It will pass through most Berkefeld V-cylinders and many Berkefeld N-cylinders, but is retained by most of the fine-textured W-cylinders. It is not destroyed by arsenic compounds. Ultra violet light destroys the tumor cells without destroying the causal agent. X-rays have little effect either on the agent or the sarcoma cells.

"These various features seem sufficient to identify it as a living organism in distinction from a ferment." (Rous, l.c., p. 204.)

"Growth of the tumor, dissemination, injury to the host, immune processes all are referable to these cells suddenly endowed with new properties." (Rous, l.c., p. 204.)

"During the last three years more than a thousand fowls, with or without the tumor, have been kept together in close quarters, yet no instance of natural transmission has been observed." (Rous, l.c., p. 205.)

"In conclusion it should be stated that the experiments with chicken sarcoma have not yielded a method whereby a causative agent can be separated from the tumors of rats and mice. But they clearly prove that the characteristics of malignant tumors in general are compatible with the presence of a living causative agent. Such a cause for them seems, indeed, far from improbable." (Rous, 1912. Proc. Am. Phil. Soc.)

Subsequently Rous and his associates demonstrated that two other chicken sarcomas—a slow-growing osteochondrosarcoma (No. VII) and a peculiar sarcomatous tumor with innumerable blood rifts (No. XVIII) are due to filterable viruses. These viruses differ in a number of ways from the virus of his sarcoma No. I—that of No. XVIII, for example, is destroyed by drying, and by glycerin, and No. VII survives drying only when frozen. Cultures from these tumors on various media were also sterile as regards bacteria.

Two replies were open to objectors, and there were many. Some said, especially in the beginning: The disease is not a genuine sarcoma but only a granuloma. Others said: Possibly some tumor cells more resistant than others have escaped the heat or cold, or have passed through crevices in the filter and have multiplied in the tissues after injection. But fair-minded investigators are now generally agreed that the disease is a sarcoma and, in answer to the second objection, Rous ground up his chicken sarcoma cells, dried them over sulphuric acid, pulverized them, kept this dry dust for seven months, and yet with it was able to produce the disease. *The cell, therefore, is not the parasite, but some other living thing may be.* Where it passes the rest of its existence is not known. As long as we do not know what this something is we may very well call it the virus, or the agent, as Rous has done.

This work on chicken sarcoma has been verified in Japan, including the

filterable virus, by Akira Fujinami, who tells me that he discovered the tumor independently but that Rous published first.

IV. WORM CANCERS

As leading up to the specific experiments I shall mention under this heading, it is well to say that, owing to the labors of many observers covering a series of years, and especially to those of Borrel, attention has been drawn repeatedly to the suspicious close association of various parasitic worms with papillomas, epitheliomas, carcinomas and sarcomas in man and animals, e. g., the Egyptian disease of the bladder known as Bilharzia which frequently ends in carcinoma, is always associated with *Schistosomum haematobium* (*Distoma haematobium*), a trematode or fluke, passing the other part of its life in water snails of the genus *Bulinus*. Intestinal cancer in certain districts of Japan, more common than elsewhere, is associated with another fluke (*S. japonicum*), the larval form of which lives in another snail. Cancer of the intestine in the horse is associated (Borrel) with the nematode *Sclerostoma*; breast cancer of the mouse is frequently associated with a nematode (Borrel, Haaland) and probably much oftener than has been recorded; several times cancer in man has been found associated with *Trichina spiralis* (see pp. 33-35, Fibiger IV, Biolog. Medd. I, 10); liver sarcoma of the rat is associated with the larval form of a *Taenia* of the cat; and so on. We have also destructive nematode tumors in plants. One is due to *Heterodera radiculicola*. It occurs on the roots of a great variety of plants and is more injurious than crown-gall. Structurally, the tumor is a soft, perishable, small-celled connective-tissue hyperplasia containing a great many large multinucleate giant cells. Many plants are killed by this tumor, and many others are dwarfed so badly as to be worthless. It occurs on a multitude of hosts in many parts of the world and has not received the attention it deserves. Other destructive above-ground plant tumors are due to nematodes of the genus *Tylenchus*. These occur on wheat, clover and other plants. Non-verminous forms have also been incriminated, e. g., cancer of the face (12 cases) and of the breast (6 cases) associated with the mite *Demodex* (Borrel, Asso. fr. p. L' Etude du Cancer, 1908-1909.) The last instance of association I recall is the recent discovery that Hodgkins' disease, which frequently ends in lympho-sarcoma, is associated with cells of the protozoan *Endameba dysenteriae*. (Kofoid, Boyers and Swezy. Jour. A. M. A., May 27, 1922.) You all know how frequently cancer develops on syphilitic and tuberculous lesions,

but I am to deal here only with experimental evidence.

a. Fibiger's Rat Carcinoma Due to Cockroach-Nematodes

In 1913 Johannes Fibiger, Professor of Pathological Anatomy and Director of the Anatomical Pathological Institute of the University of Copenhagen, after a research covering more than two years, announced that he had produced in the stomach of rats inflammatory reactions, numerous papillomas and a few carcinomas by feeding them nematodes found in the muscles of a cockroach where they are coiled up and encysted like *Trichina spiralis* in the muscles of the pig. Since that date Fibiger has pursued his researches unweariedly with remarkable results which are now perfectly well established.

The story of his investigations, presented in a dozen lucid papers, is as fascinating as a romance.

The nematode lives chiefly in the pavement epithelium of the stomach of the rat. It here reaches sexual maturity and evacuates ripe eggs (containing embryos) which are liberated by desquamation of the epithelium and passed with the excrements. The feces of infected rats nearly always contain eggs but never free embryos. When such feces are consumed by cockroaches the embryos are liberated from the egg and wander into the striped muscles of the prothorax and the limbs of the insect, where after six weeks or more the larvae are found coiled up in spirals.

When such cockroaches are eaten by rats the larvae are freed from their capsules and wander into the squamous-cell epithelium of the cardiac part of the stomach or more rarely into the epithelium of the esophagus, tongue and mouth where in about two months the females begin to lay fertile eggs which soon find their way into the feces.

In most cases, especially if the rats are examined early, only inflammatory reactions and papillomas are found. But even as early as 1913 Fibiger had found 5 cases of cancer in rats fed on nematode-infected cockroaches and he has found many since. He says of these early observations:

"In 5 laboratory rats fed on cockroaches (in 4 cases *P. americana*, in 1 case *P. orientalis*) microscopical examination of the cardiac portion of the stomach showed processes which differed from those in the other rats. The changes, in fact, here appeared to be true cancerous growths, the mucous membrane and submucosa having changed into a tumor tissue of quite the same type as is generally found in true squamous-celled carcinoma in man.

"In two of these rats carcinomatous metastases were observed in a lymph gland and in a lung respectively; in a third case the urinary bladder contained papillomatous growth which was probably a metastasis too. Notwithstanding a very careful examination of serial sections

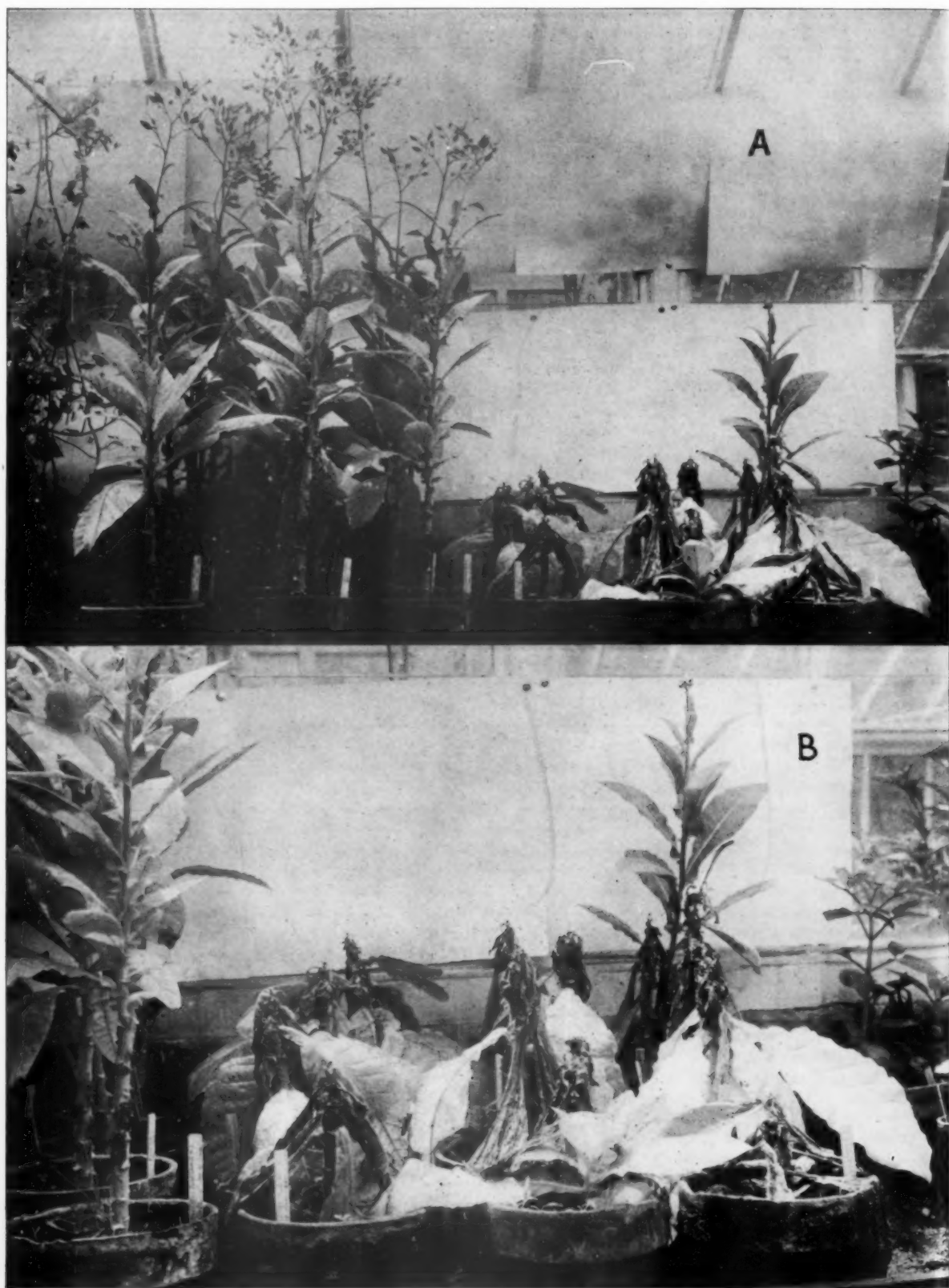


Fig. 5—**A**—Photo of tobacco plants, all of which were inoculated with *Bacterium tumefaciens* at the same time and in the same way except that those at the left were pricked in semi-mature tissues on an internode six inches below the top; and those at the right, in very soft tissues in the region of the terminal bud. Photographed at end of three months, that is, three months earlier than the condition shown on the right side of figure 4.
B—A closer view of the right side of **A**. Inoculated Feb. 20, 1922. Photographed May 19, 1922. The plants are in a

much worse condition than they were on May 1, but not so bad as on September 8.

These experiments and the preceding on *Bryophyllum* combat Levin and Levine's assertion, *J. Cancer Research*, 5:256, et seq., that "the crown-gall is usually a benign tumor and only rarely does it act in a manner analogous to a malignant tumor in an animal," and show that, like sarcoma in animals, the disease is most destructive in the soft tissues of young plants, the host reaction in the plant as in the animal being a variable one.

neither nematodes nor eggs were found in any of these metastases, being thus metastases in the most strict sense of the term.

"By these investigations carcinomatous tumors giving rise to metastases were produced experimentally for the first time, and the hypothesis put forward by Borrel and Haaland was thus verified, as it has now been proved that nematodes play a causal part in the development of cancer in rats."

Dr. Fibiger was led to make these studies by finding in 1907 in the stomachs of three captive wild rats (*Mus decumanus*) enormous papillomas associated with a nematode and showing carcinomatous tendencies. These rats which belonged to the Anatomical Pathological Institute were probably imported from Dorpat (Russia). This discovery led to the examination of numerous Danish wild rats and of black and white rats from various laboratories, but neither papillomas nor nematodes were to be found. He was then led to consider another possibility: viz., that this nematode might have a second host and following Osman Galeb's discovery (C. R., T. 87, 1878) he sought for it in the cockroach (*Periplaneta orientalis*). The first search was made on wild rats in a locality where *P. orientalis* was very abundant, but all the examinations were negative; neither could the tumors be induced by feeding healthy rats with cockroaches from this locality. A little later Fibiger discovered, quite against expectation, what he was searching for in another species of cockroach (*P. americana*) from a sugar refinery where both rats and cockroaches were abundant. Out of 61 wild rats (*Mus decumanus*) caught in this locality 40 showed the nematode in the cardiac part of the stomach. In 18 of these there were pathological changes, and cancers were found in nine. Moreover, of 57 black and white rats fed on *Periplaneta americana* from this sugar refinery the worm was found in 54. In 37 of these 54 rats there were pathological changes, and cancers were found in 7. Previous to this, 1,144 rats of several species from other Danish localities had been examined without finding any nematodes or any tumors. The results obtained left no doubt as to the second host or as to the responsibility of the nematodes for the tumors. Fibiger then fed 18 cockroaches on the feces of infected rats and obtained nematode infections in the muscles of 17. He also fed 9 cockroaches on nematode eggs and obtained 9 infections, whereas the muscles of 101 non-fed control cockroaches were free from nematodes. Fibiger also showed that a second host is necessary. The round worm must pass from the rat to the cockroach, or a similar host, before it can again infect rats.

Up to 1918 the nematode, first called *Spiroptera neoplastica* and now

following Ransom, *Gongylonema neoplasticum*, had been bred about seven years, using not only the large light brown cockroach, *Periplaneta americana*, but also the black-brown species, *P. orientalis*. The nematode may also be bred in meal worms and in German cockroaches, but less satisfactorily.

Feeding experiments have been made on wild house rats (*Mus rattus*), black and white laboratory rats, Norway rats (*Mus decumanus*), Alexandria rats (*M. alexandrinus*), and bastards of Norway rats and black and white rats; also on white and on black and white laboratory mice, wild house mice (*Mus musculus*), forest mice (*Mus sylvaticus*) and Japanese waltzing mice. The nematode is transmitted very readily to all of these rodents. It has been transmitted also to rabbits, guinea pigs, squirrels (*Sciurus vulgaris*) and hedgehogs. In all of these animals it lives in the squamous epithelium of the upper part of the alimentary canal, but so far as I have read cancer has been produced with it only in rats and mice, and most successfully in rats.

More than 900 animals have been used in these experiments and the results obtained on many of these animals remain to be worked over in detail but up to 1921 the nematode cancer had been found in the fundus of the stomach of more than 100 rats. This is the more astonishing because cancer of the stomach is a rare disease in rats, except as related to this parasite. Five of the rats also had cancer of the tongue, a very rare disease, except as caused by this worm. The nematode cancer had also been produced in the fundus of the stomach in white mice but in 3 only out of more than 200 inoculated. Metastases (mostly to the lungs) had been found in 6 out of 33 rats (1921) and in 2 of 3 mice, and this mouse tumor without the nematode had been transplanted through several generations of mice.

These statements, however, do not express the whole truth, for, if we exclude rats that die early of intercurrent diseases, e. g., broncho-pneumonias, or as a result of the primary infection, and consider only those which survive the nematode feedings for six weeks or more, and are of susceptible races, the number developing cancer then exceeds 50 per cent.

If too many cockroaches are fed, the rats die soon after the feeding from inflammatory processes and hemorrhage (acute gastroenteritis). If their muscles are well infected, three to five cockroaches are considered enough for each rat.

From 1913 on, for some years, owing to a fire, Fibiger used only *Periplaneta orientalis* for his feeding experiments, but during the eighteen months

immediately preceding the publication of his 1918 paper he again bred *Periplaneta americana* regularly and now uses it altogether for his infections, because it is more resistant than *P. orientalis* which is apt to die if overfed with nematode eggs from the rat feces. He now often feeds his rats the encysted worms dissected out of the muscles into normal salt solution rather than the cockroaches themselves, since this enables him to know the number of worms fed and especially to infect the tongue.

The natural host of this round-worm is *Periplaneta americana*, indigenous to South America and the West Indies, where both the cockroach and the rat have been found harboring the parasite. It is believed to have been imported into Denmark from the Danish West Indies on sugar ships. Except in this one species and in this one locality (a sugar refinery which was subsequently burned, destroying both cockroaches and rats) Fibiger has never seen it in Denmark.

In support of his belief that the worm is of American origin, Fibiger states that he has examined 1,300 Danish wild rats, nearly 500 laboratory rats from Denmark, England, Holland and Germany and enough Alexandrine rats to total 1,800 without finding the worm. He also cites confirmatory evidence from Wassink who examined more than 1,000 wild rats from Amsterdam without finding it, but among 625 rats caught in ships Wassink found 5 containing this nematode and these five came from ships in the South American service. He also found it in 16 out of 40 rats caught in Suriname (S. A.) Wassink examined also great numbers of cockroaches from Amsterdam but found the nematode only in *P. americana* and *P. orientalis* originating from a sugar refinery which formerly received West Indian sugar and there the parasite spent the other part of its life in mice, there being no rats in this refinery. The worm was not found in either cockroaches or rats taken from ships in the East Indian trade, but has been found in cockroaches caught in Parimaribo. Fibiger himself found it in wild rats and cockroaches caught and sent to him from St. Croix (V. I.)

The number of worms in cockroaches which have been fed on the feces of infected rats varies greatly; there may be none, a few, several dozen, or several hundred. As a rule Fibiger used the cockroaches 85 to 90 days after beginning the feedings with infected rat feces, but only a small part of the nematodes succeed in obtaining a lodging in the tongue, throat, gullet or stomach of the rat.

Fibiger cut many entire rat stomachs in series and often found two to five

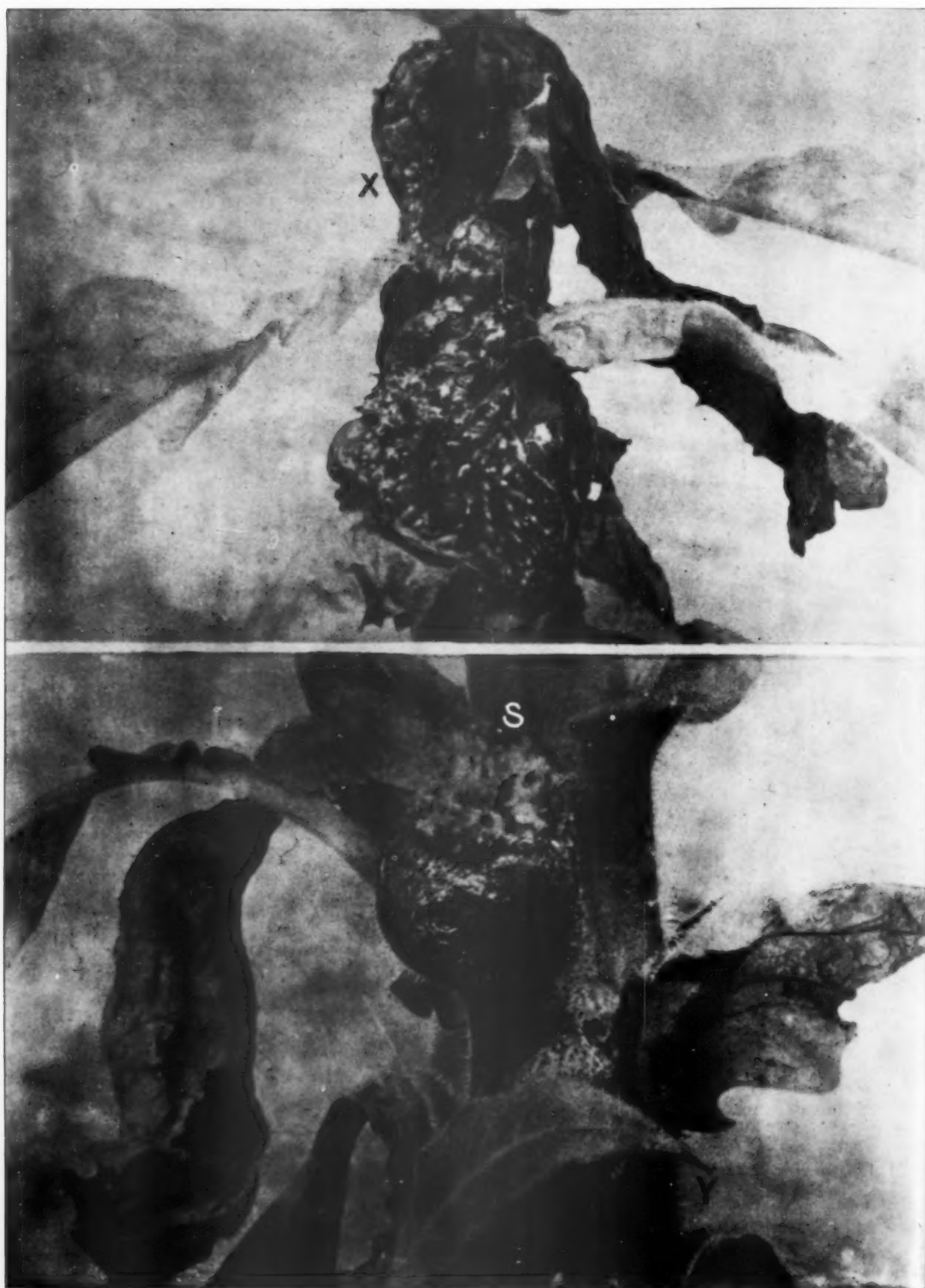


Fig. 6—Two tumors from the terminally inoculated tobaccos shown in figures 4 and 5, both of which are embryomas. The lower part of the upper one is full of roots and there are also

roots at **X**. The upper part of the lower one is full of shoots (under **S**). Most of a second tumor at **Y** has decayed. Photo, May, 1922, X3.

independent small centers of cancerous growth (squamous cell carcinoma with many epithelial pearls). These cancers, therefore, are often multicentric. "Most frequently a larger tumor focus was accompanied by several smaller foci of approximately equal size."

Fibiger states distinctly and emphatically that he considers the cancerous process as entirely distinct from the inflammatory and papillomatous one.

"A mon avis le carcinome est dû à un processus à part, n' évoluant que dans des conditions spéciales et s'associant comme complication indépendante et essentiellement différente à la simple prolifération épithéliale hyperplasique et hétérotopique, dont il ne représente nullement le point terminal.

"De même on constate des phénomènes inflammatoires et de la papillomatose dans tous les estomacs infectés par les spiroptères, mais il n'y a pas de rapport entre le degré de ces phénomènes d'un côté, et l'existence et la fréquence des carcinomes de l'autre. Les phénomènes inflammatoires et la papillomatose peuvent être très prononcés dans un estomac sans qu'il ait de carcinome, et vice versa. Il ne faut donc pas attribuer à l'inflammation une influence quelconque sur la croissance du carcinome en plein développement. Nos connaissances actuelles sont insuffisantes, pour juger la question de savoir si l'inflammation ne jouerait pas un rôle tout à fait au début, avant que la disposition et la transformation des cellules aient pris les caractères morphologiques typiques du carcinome, mais il paraît probable que l'inflammation est plutôt un phénomène secondaire ou en tout cas coordonné à la cause qui détermine l'évolution du carcinome."

Fibiger's experiments indicate that there is a species, a race, and an individual predisposition to carcinoma. He suggests that there may be also a predisposition of special organs, since he has examined several hundred rat-esophaguses infected with the cockroach nematode but has never found a carcinoma although the organ is identical in structure with the cardiac part of the rat's stomach. Also in white mice the digestive tract is very resistant to the nematode cancer while the skin is extremely subject to tar-cancer, so that it is doubtful if we may speak of a general cancerous predisposition. His experiments lend no support to the belief that carcinoma is only a disease of old animals.

"Jusqu'à présent j'ai rencontré le carcinome aussi souvent chez les animaux jeunes que chez les animaux âgés."

In a few cases Fibiger also observed sarcoma-like proliferation of connective tissue (German paper of 1913.)

No nematodes were found in any of the metastases. In other words, the carcinoma once started is able to continue without the presence of the nematode. In case of the mouse cancer produced by the nematode, up to 1919, Fibiger had transplanted it through four generations without the presence of the worm. The question then arises: Is the nematode the cause? or does it only produce an irritation in which some unknown cancer virus may take root, if

present? It is not unreasonable to suppose the latter may be the case because in by far the larger proportion of his inoculated rats inflammatory reactions which soon subsided, or simple papillomas, were all that Fibiger observed. Moreover, rats whose stomachs have contained egg-laying nematodes for a very considerable period may subsequently be found free from them and with normal stomachs. Even in rats that lived for a long time after the feedings and were known to be infected for many days, because eggs were found regularly in their feces, inflammatory reactions and papillomas were all that Fibiger found in nearly 50 per cent of his cases.

I shall have more to say about this when I come to discuss the cat-tape-worm rat-sarcoma and will only add here that in Fibiger's rats, in all cases, the carcinoma begins not contemporaneously in the whole irritated area, as we might expect it to do, but only in very limited portions of it, minute spots, in comparison with the whole nematode-parasitized area. This is true also of the tar cancers. Borrel believes that there is a distinct cancer parasite or virus of which the nematode is only sometimes the innocent carrier.

Fibiger's chief objection to this view is that there appears to be a proportional relation between the number of worms and the development of the carcinoma, the rule being: Few parasites, feeble changes, whereas a few worms should suffice, he thinks, to bring about a bacterial infection just as well as a large number.

He brings another objection, viz., that when the round-worm *Trichodes* bores into the stomach wall making numerous passages there results nothing comparable to what he has found, although, if wounds are necessary to let in a supposititious bacterial parasite, wounds made by one species of worm ought to serve as well as those made by another worm. This would certainly be a strong objection if based on a sufficient number of observations and if *Trichodes* also caused prolonged favorable inflammatory reactions, which does not seem to be the case, and, finally, and especially, if the supposed cancer virus is normal to the surface of the rat and mouse so that any kind of wound would be sufficient to introduce it, but, on the other hand, it might be only normal to and perhaps only occasionally present in *Gongylo-nema* and never present in *Trichodes* and never normal to the surface of the rat, or, if so, as would seem more likely, able to enter only into a weakened organism through a specially prepared surface which would entirely alter the situation and destroy the force of his argument. To Menetrier, as to

Virchow, cancer is not a primitive morbid form but the end of multiple anterior and preparatory pathological states.

Microscopically visible bacteria as a cause of these tumors appear to be ruled out, because in only a very few cases was Fibiger able to find any.

Fibiger admits the possibility that the carcinoma may be a special process, subsequently grafted on the papilloma and having an etiology of its own, but against this he raises the possibility that the carcinoma begins in just those portions of the proliferations which have been exposed to the strongest action of the nematode poison which, he assumes, may be of variable virulence. Here then are the two aspects of the problem, both theoretical, and, as he says, related back to the whole problem of carcinoma development.

b. Kopsch's Frog Tumors Due to Angleworm Nematodes

In 1919 Dr. Fr. Kopsch, privatdozent and II prosector in the Anatomical Institute of the University of Berlin, published an octavo, 130 page monograph illustrated by 23 text figures and 23 colored plates containing 107 figures, describing in much detail tumors of the frog (*Rana fusca*) which he had produced in large numbers in various organs by feeding them angleworms containing the nematode *Rhabditis pellio*, which has been found also in inflammatory conditions in man.

Kopsch's interest in the frogs, at first, was purely anatomical and morphological. In the summer of 1915 he says he bred *Rana fusca* in considerable numbers to complete certain developmental studies, but a hitherto unobserved disease put an end to his studies by destroying the frogs. Although he had bred frogs for many years this was the first time he had had any trouble. On dissecting these frogs he discovered numerous whitish nodules in the esophagus, stomach, duodenum, liver, pancreas and various other organs and each of these nodules contained one or more nematodes, usually only one. He had fed these frogs for two months on angleworms from a certain locality and on dissecting angleworms from this region he found the same nematode. In the course of two to seven months nearly all of the frogs contracted the disease. The frogs longest infected showed the most striking evidences of disease.

The following year (1916) Kopsch bred more frogs and fed them exclusively for three and one-half months on angleworms containing the nematode, and again in many frogs he obtained the tumor-disease.

The sick frogs refused to eat, often became lean and listless, vomited food and slime containing nematodes, lay

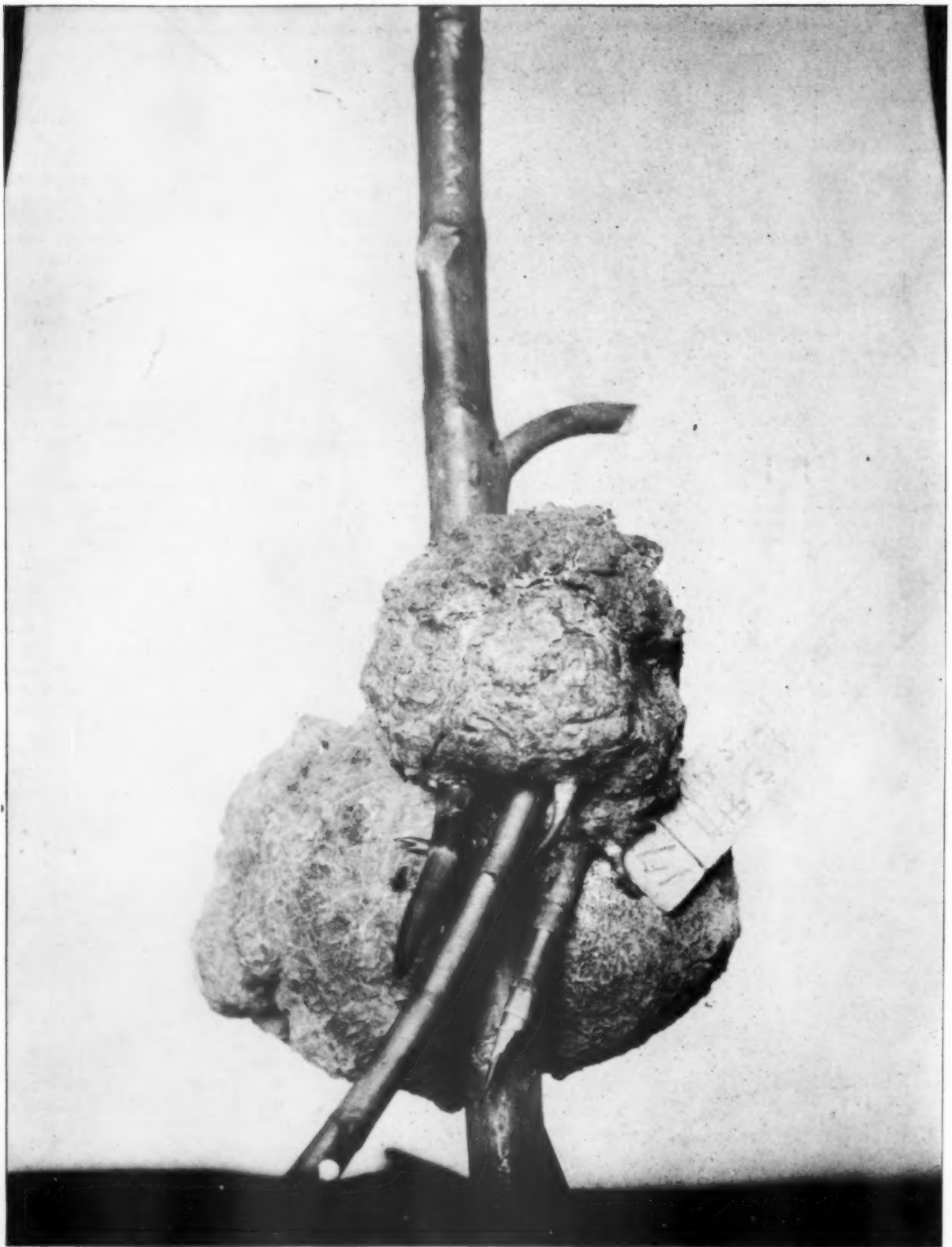


Fig. 7.—Crown-galls on *Ficus elastica* (common ornamental rubber tree) due to *Bacterium tumefaciens* (hop strain). The lower tumor resulted from inoculations made February 5, 1921, by needle pricks in the region of the terminal bud. They missed the growing point and the tumor contains no shoots. The smaller tumor resulted from a reinoculation made a month later by means of three needle pricks and has given rise to eight shoots, the two smaller ones are under the arrow. This is what Michael Levine said could not be done, either on

Bryophyllum or *Ficus elastica* (*Mycologia*, Jan., 1921, p. 7). Photo, Feb. 1, 1922.

The buds in *F. elastica* are concealed by twisted bracts and are very difficult to hit with a needle, so that the plant is not well adapted for such experiments, but, contrary to Levine's supposition, it does not react differently from other plants and by making enough experiments it ought to be possible to reach the bud in such a way as to produce a tumor containing many shoots.

flat on the earth, finally with the head down, or motionless on the back in the water, suffered at times from tonic spasms, became rachitic (probably from the one-sided diet) and finally so weak that they had to be fed by hand and in this way were kept alive a few weeks longer. A few of the old frogs suffered from internal hemorrhage. Only one of the frogs lived as long as fourteen months. Many died or were killed too soon for any appearances suggestive of cancer.

Frogs fed on infected angleworms may contain an extremely variable number of the worm nodules, one or two or a few up to 200 or more. This is probably because young angleworms contain few or none of the nematodes. The older worms contain a variable number of the nematodes distributed in various organs.

The worms in the frog are enclosed in a capsule at first but after some months the capsule disappears and then the tumor becomes locally malignant.

Most of Kopsch's feeding experiments were done on young frogs beginning soon after the change from polywog, but he fed enough old frogs to know that they also are susceptible. Mice could not be infected. He continued his experiments in 1917, but only the results of the first two years are given in the monograph, which is based on the findings in 44 frogs, other frogs in the series being rejected because they died or were killed too early to obtain interesting results. The signs of the disease did not begin until after two or three months.

A great many serial sections were cut from various organs of many of these frogs.

In the 1916 frogs (28) there was nothing discoverable in the way of adenomas or cysts until the fourth month after infection, but heterotopic glands appeared much earlier and heterotopic epithelium was detected as early as the fourth week. These down-growths were extraordinarily numerous in some of the frogs (29 in No. 13). Adenomas were also numerous in some of the older frogs (54 in No. 16). After about 5 months the capsules are disintegrated and absorbed and the tumor cells are then free in the tissues and locally malignant, reaching out irregularly and compressing and destroying surrounding cells. The liver from frog No. 29, which was nine and one-half months old contained 26 worm nodules, of which 21 had lost their capsule and had become locally malignant.

No convincing evidence of metastasis is furnished but it is likely that further studies may furnish it.

Kopsch has not done as much work as Fibiger, nor carried his investigations as far, but what he has done is exceed-

ingly interesting and points in the same general direction. His text is not altogether convincing as to carcinoma and sarcoma and most of his figures indicate to me only inflammatory changes, benign adenomas, heterotopic growths of epithelium, etc., but in a few cases in the frogs longest infected he figures and describes changes which must perhaps be interpreted as beginning carcinomas with epithelial pearls. In a few cases he also obtained changes which he interprets as beginning sarcomas. He should furnish more convincing evidence both of deep invasion and of metastasis, and probably will do so. His work, if it stood alone, would not be entitled to as much weight as it must receive, following, as it does, Fibiger's convincing studies.

c. *The Rat Liver-Cyst Sarcoma Due To a Tapeworm of the Cat*

In 1910 (An. de L'Inst. Past.) and again in 1912 in his paper before the first International Congress of Comparative Pathology, Borrel of the Pasteur Institute in Paris called special attention to this rat liver-cyst sarcoma in which he said he had been interested for nearly ten years, having found eight cases of it. His labors and the concordant labors of Regaud, Saul, McCoy, and Bridre had resulted up to that time in finding 50 cases of the disease.

The life cycle of this parasite is as follows:

Taenia crassicolis, the perfect form of the worm, lives in the intestines of the common cat. The eggs of the worm are voided in the feces of the cat, which are eaten by rats. In the stomach of the rat the eggs of the worm hatch and the young larvae bore through the walls of the stomach and intestine and lodge in the liver. A wall of fibrous protective tissue, the cyst, is formed about the young worm, which gradually elongates in a close coil to a length of several inches and takes on the larval form known as *Cysticercus fasciolaris* in which condition it remains, so far as we know, until the rat is eaten by a cat, whereupon the larvae complete their changes, becoming in the cat's intestine the perfect egg-laying *Taenia*. The yellowish white cysts in the rat's liver grow with the growth of the worm until they are often as large as a cherry, but even when there are several to many they do not seem to injure the rat very much unless a sarcoma develops.

Recently the experimental study of this disease has been undertaken in a large way by Bullock and Curtis at the Crocker Institute for Cancer Research in New York with striking results (Proc. N. Y. Path. Soc., Oct.-Dec., 1920). At the present time they have several thousand rats which

have been fed with the eggs of this tapeworm and all of which presumably are infected. The experiment has been going on only about three years but from these rats during this short time more than 250 typical malignant sarcomas of the liver have been obtained, many of them showing numerous metastases to the omentum, lungs and other organs.¹ I have never seen a more remarkable collection of illustrative material, nor do I think there is a more interesting experiment going on anywhere in the world at the present time. It is unfortunate that so little money should be available for this and similar important undertakings. Rich men offer large sums for cancer cures only to be overwhelmed with fraudulent claims, but the men and women who are devoting their lives to researches likely to throw light on various phases of this difficult problem, and working desperately hard, are left to get along any old way. I know five or six places in this country where a few thousand dollars is very much needed and would help cancer research amazingly.

These rat sarcomas always begin in the cyst-wall, that is, in close proximity to the feeding *Cysticercus* and the close-fitting cyst-wall is subject, of course, to all its bitings and excretions. Once started the sarcomas grow very rapidly, are palpated without difficulty and soon destroy the animal. There is the closest relation between the worm and the tumor but there are several very curious facts in connection with the disease which are hard to interpret on any other hypothesis than that formulated by Borrel, who says:

"Le cysticerque n'est donc pas le parasite du cancer, il ne peut être considéré que comme le porte-virus, l'agent d'inoculation de quelques microbes que nous ne connaissons pas encore. * * *

"Demodex, cestodes, nématodes, sclérostomes, ne sont pour nous que des agents de localisation; ils sont dans d'autres cas remplacés par: brûlures, corps étrangers, lésions ulcéreuses, agents physiques ou chimiques capables de préparer le terrain à un virus cancéreux, et ce terrain lui-même lorsqu'il s'agit de cancers épithéliaux n'est réellement préparé et apte à être ensemencé qu'à partir d'un certain âge."

These curious facts to which I have referred and which appear to sustain Borrel's hypothesis are: (1) The rat's liver may be full of cysts (a dozen or more) each containing the parasitic worm, and yet no sarcoma may develop; (2) when the tumor does appear, it occurs not in each one of these worm-irritated cysts but as a rule only in one; exceptionally in two or three, very rarely in four or five; (3) the beginnings of the sarcoma are even very much more restricted than this would indicate in that only one small area of the cyst wall or at most a few small spots are at first involved. Moreover, while Bridre saw the *Cysticercus* in 8,000

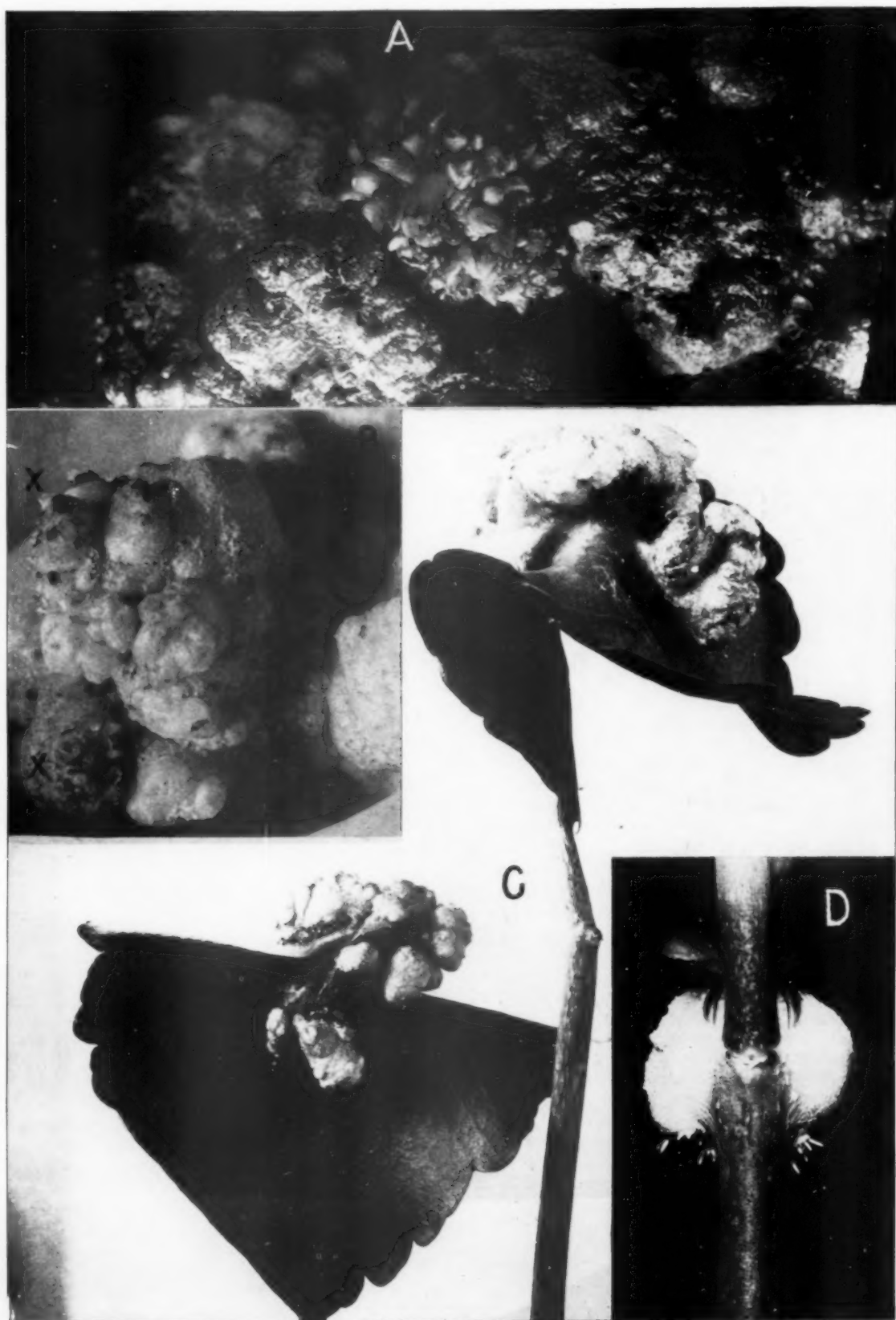


Fig. 8.—Crown-galls on *Bryophyllum calycinum* showing abortive shoots, abortive roots, and distortions of leaves due to the growth of the tumors. Hop strain. Needle prick inoculations of 1920 and 1921.

A—Bunch of dwarfed shoots in an axillary tumor. Inoculated May 14, 1921. Photo, Aug. 15, 1921, x5. Only about one-fifth of the tumor is visible. **B**—Groups of roots at **X X** in a midrib tumor. Inoculated June 23, 1920. Photo, Nov. 18,

1920, x5. **C**—Leaflets showing distortions due to midrib tumors. Inoculations of 1920. Natural size. **D**—Roots developing from an axillary stem-tumor. Inoculated about two months. Photo, June 4, 1920.

For further evidence of effect of crown-gall stimulus on *Bryophyllum* see Jour. Agr. Research, July 15, 1921, and for M. Levine's paper see Bull. Torrey Bot. Club, 46: No. 11, 447-452, 1919.

rats out of 20,000 examined, (Borrel) he observed only 20 cases of the sarcoma. Had these worm-infested rats been held in captivity for some months he would undoubtedly have found a much larger number of sarcomas, but all this being admitted, the great mountain fact squarely in the way of those who would explain the sarcoma as due directly to the activities of the *Taenia* is that out of thousands of liver cysts only a very limited number even in susceptible rats develop the sarcoma whereas every one of the cysts encloses a parasitic worm and is exposed so far as we know to the same verminous irritation.

The fact that all the *Taenia* eggs used in the experiment at the Crocker Institute have been obtained from the feces of one cat are not an insuperable objection to Borrel's hypothesis for several reasons: (1) assuming the virus to come from the *Taeniae* some eggs might carry it and others not—all *Anopheles* do not carry the malarial parasite, all *Stegomyia* do not transmit yellow fever; (2) the virus might be encountered first in the rat's intestine, free, and then, if not very abundant, it would be carried in by some larvae and not by others; (3) the virus might not be present at all in the digestive tract of some rats and then there would be no sarcomas no matter how many cysts; suppositions which correspond very well to the observed facts. On the other hand, if the sarcoma is due directly to the poison of the *Cysticercus* either it must be variable in its nature or else more abundant in the sarcomatous cysts, which would mean a larger worm.

Early extra cystic tumors have not been observed by Bullock and Curtis. Of the 85 cases reported on by them in 1920 metastases were distinguishable in the gross in 52. Other statements from Bullock and Curtis are as follows:

Young rats are most susceptible. Ninety per cent of the 43 tumors tested were transplantable. One strain of 600 rats was discarded because of its great resistance to the *Cysticercus* infection. The tumor-bearing rats, moreover, were nine and one-half to eighteen months of age, of both sexes and of five strains. The larvae in the tumor-bearing cysts were usually alive—always unless necrosis had supervened.

"All the tumor-bearing rats presented multiple cysts in the liver, varying from 6 to 84 in number. In a high percentage of these animals only one of the cysts was primarily involved in the malignant process." (Bullock and Curtis, *loc. cit.*, p. 168.)

V. EXPERIMENTAL COAL TAR CANCERS

These experiments grew out of the long observed and often recorded fact that cancer is prone to develop on special types of irritation due to prolonged contact with tar or soot or some

of their products (Tar-workers' cancer, Chimney-sweeps' cancer, etc.) Numerous cancer workers in the early part of this century treated the skin of experimental animals for several weeks or months with coal tar in the hope of producing cancer, but all of these experiments failed, apparently because they were not continued long enough.

a. Experiments of Yamagiwa and Ichikawa

Beginning in the autumn of 1913, Dr. Katsusaburo Yamagiwa, a former student of Rudolph Virchow, founder of the Japanese cancer journal, *Gann*, and professor of general pathology and pathological anatomy in the University of Tokyo with Doctor of Vet. Med. Koichi Ichikawa, also of the Pathological Institute of Tokyo, continued with great pertinacity several series of coal tar paintings some of which finally resulted positively. The immediate incentive to this work is said to have been the brilliant success of Fibiger's cockroach-nematode rat feeding experiments already detailed. They selected rabbits as their experimental animal and finally settled upon coal tar as the best substance to use. This was put on rabbits' ears, an organ peculiarly free from any suggestion of carcinomatous growths. By painting the inner or outer surface with coal tar every second or third day for a year (more or less) they finally obtained many papillomas (called by them foliculo-epitheliomata or hair follicle canceroids) and a few undoubted keratinizing carcinomas of a mild type (Mitt. aus der Med. Fak. d. Kaiserl. Univ. zu Tokyo, Bd. XV and XVII). Menetrier and Surmont in Paris have obtained the same results (*Bull. de l'Asso. fr. p. l'Etude du Cancer*, Dec., 1922, and Jan., 1923.)

b. Experiments of Tsutsui

In 1918 Dr. Hidejiro Tsutsui, professor of general pathology and pathological anatomy in the medical high school in Chiba, reported that he had obtained similar results on mice (*Kuenstliche Erzeugung von Cancroid bei der Maus*, *Gann*, 1918, Bd. XII, pp. 17-21.)

Tsutsui used stone-coal tar and English mice, painting the skin of the back every three or four days with a Japanese writing brush. His seven experiments included 259 mice, 192 of which died before the 100th day, apparently poisoned by the tar as a result of licking the painted spot, and these are not counted in the results. The response to the paintings at first was loss of hair, and a smooth, injected appearance of the skin. In time, the spots became hyperkeratotic, rough, dry and scaly. Those mice that lived for more than 100 days developed warty and knotty tumors with the structure of benign papillomas but the base of some of these

became transformed into invasive carcinomas of the cancrroid or horn-tumor type and lung metastases were observed in two cases. The longest painting was 166 days. Of the 67 mice which survived the paintings more than 100 days, 16 developed carcinomas and one a spindle-cell sarcoma.

c. Danish Experiments

Fibiger then commenced a series of coal-tar paintings on white mice the results of which he published in 1921 (*Biol. Meddelelser*, III₁). His results are entirely confirmatory of the preceding and leave no doubt that cancer will develop in a certain proportion of coal-tar-painted mice if the experiments are continued long enough. He got nothing definite until after many days. In two of Fibiger's cases he observed metastases in lymph glands, and in two cases the tumors were transplantable. The malignant tumors obtained were either typical keratinizing carcinomas or mixed carcino-sarcomas. They bore no definite relation to the amount of inflammatory reaction.

d. Dutch Experiments

In November 1921, Dr. Deelman, director of the Leeuwenhoek laboratory in Amsterdam, communicated (*Ned. Tijdschr. v. Geneesk.*) the results of a series of coal tar paintings on white mice begun after the publication of Tsutsui's experiments and before Jensen had published.

He depilated the skin of the back with Beyersdorff's depilatory and tar-painted the naked skin three times a week for many weeks. Nothing was visible for two and one-half months. After that redness appeared and papillomas or small flat spots developing as ulcers. At first the tumors were benign in structure but subsequently they became malignant. The malignant tumors appeared in two forms—direct as carcinomatous ulcers or the same with a papilloma as a preliminary stage. Deelman obtained both carcinoma and sarcoma and the latter he was able to transplant through 11 generations. Good illustrations are given showing the progressive stages of the disease on several mice and the appearance of the carcinomas and sarcomas in section under the microscope. Invasion, destruction of surrounding tissues and metastases were observed. His 48 treated mice were divided into two equal lots: one lot was painted with coal tar from a horizontal apparatus and the other lot with tar from a vertical apparatus. Both tars produced cancers but tar from the vertical apparatus was very much slower in its action. Some of his mice died early and there is no statement of the per cent that developed cancer, but because of this omission we may assume it to have been small.

Dr. Deelman has published three additional papers (Klin. Woch. Jahrg. 1, No. 29 and Ztschr. f. Krebsforsch. Bd. 18 and 19.) The most important new thing he has discovered is that, in early stages, tar cancer in the mouse grows by *apposition* as well as by *invasion*, that is (1) *aus sich heraus*, and (2) horizontally in all directions by "cancerous conversion" of the surrounding epithelial cells. Deelman's observations rest on a wealth of material, viz., on 62 tumors sectioned in series from the backs of 18 tar treated mice, all in early stages of growth. He is also positive the cancers begin at the same time in many cells and are often multicentric. In other words, he rejects Ribbert's views and sides with the majority (See my summary of earlier views pro and con in J. Cancer Research, 7:No. 1).

c. English Experiments

(1.) The English experiments of Murray and Woglum (7th Sci. Rep. Imp. Cancer Res. 1921) are confirmatory of those already recorded. A series of 190 mice from 3 to 6 months old were coal-tar painted in a line 1 centimeter long and 1 millimeter wide between the shoulders once or twice a week for variable periods after removal of the hair by barium sulphide paste (10 per cent sodium sulphide in water is recommended as a less poisonous substitute).

The animals were critically examined every two weeks. The initial lesions were sessile or pedunculated warts, cutaneous horns or scabby ulcers. In alternate animals the tarring was discontinued when the hypertrophies appeared. The tarring was discontinued also in the others when the growths showed signs of rapid increase in size. Some tumors which structurally could not be identified as carcinoma were autotransplanted and in this way determined to be malignant. Many animals died early of intercurrent diseases. Twenty-three developed cancers. Many of these tumors invaded and metastasized and returned after wide excision. Those mice which developed cancer received from 30 to 103 paintings, the average number being about 70. Some animals responded quickly, others only after many treatments, the time of appearance of definite malignancy varying from 16 weeks to 52 weeks. These tumors had the structure of polymorphous squamous cell carcinomata with slightly developed keratinization. Three of the tumors were successfully transplanted to normal animals. With tumor 1614 no growth was obtained in 10 normal animals although both autoplasts had grown rapidly. In this tumor and both autoplasts the growth consisted almost entirely of a spindle cell tissue with

very sparse islands of keratinization. They thus obtained a structure resembling sarcoma but the real nature of which remained in doubt because transplants failed.

They say:

"It would appear that the longer it takes to set up the malignant change the more atypical the growths will be." (p. 58).

To me the most significant features of these experiments are the successful use of autoplasmic transplantations for determination of doubtful malignancy, and the fact that in no case was a diffuse carcinomatous change produced over the whole stimulated area but only in isolated small foci, as if due to some secondary cause.

Concerning the latter point they say:

"In the majority of instances a single nodule appeared. In six or seven, two or three nodules were produced and coalesced. In two instances * * * several nodules appeared distributed along the irritated area. This can only mean that the neoplastic change is not an immediate response to a single chemical substance present in the irritant but is produced indirectly by secondary changes in small foci in the stimulated area." (p. 60).

(II) According to Archibald Leitch, director of the Cancer Hospital Research Institute, London (Brit. M. J., Dec. 9, 1922, p. 1101), a long time elapses after the beginning of tar treatment before there are any visible signs of tumor formation. In mice the beginnings are not until near the end of the third month. Previous to this there are no specific characteristics which can be labeled as precancerous. In the living mouse deep infiltration can be appreciated by the fingers after a time.

"In some of our former experiments we stopped the application of tar as soon as basal induration was evident, and we found that nevertheless the tumors went on growing with undiminished rate; the removal of the irritant did not arrest the process when once the malignant stage was reached. The failure, therefore, to detect a causal agent in a cancerous growth cannot be held as proof against the previous existence of such."

In 15 mice on which the tar treatment was stopped after four and five months and 14 of which had had small warts in evidence for a few days up to a month and another an open ulcer, the subsequent results were as follows: In 5 cases the papillomas disappeared, in 3 the warts remained simple, 1 remained doubtful (it died and was eaten by other mice) and 6 became malignant.

In a second batch of mice the tar painting, three times a week for four or five months, was discontinued before there was any sign of tumor formation. At the time the tar painting was discontinued there were 20 mice remaining with no visible sign of neoplastic reaction. The subsequent results were as follows: 6 remained negative till death, 4 developed temporary warts, 4 developed simple papillomata and 6 developed malignant tumors. The negative

cases lived 29, 42, 43, 48, 65 and 75 days after the painting ceased.

In a few cases Leitch also obtained malignant tumors by painting mice with paraffin oils (crude and more or less refined shale oils), and two of these were sarcomas.

f. Additional Danish Experiments

In July, 1922, Dr. Fridtjof Bang of Copenhagen reported to the Societe de Biologie in Paris that he had undertaken a new series of tar treatments on mice, continuing the work of Fibiger and Bang in which he had used 263 mice in 15 different series of experiments from which he had obtained 22 beginning carcinomas and 93 fully developed ones. Among the latter, five were complicated by fusocellular-sarcoma. Those mice kept in the dark developed cancers as rapidly as the others and the evolution of the disease was the same. He observed visceral and lymphatic metastases in 25 per cent of the cases and one of the metastases was a carcinoma-sarcoma. The metastases continued to develop after removal of the primary cancer.

In five series of paintings which lasted four months and more, those mice which died before the sixth month were not attacked by cancer. Of the rest, (77 in all) 97.4 per cent became cancerous, i. e., all but two.

"I have observed during more than a year mice painted with tar for periods ranging from one month to four months with results as follows:

14 mice painted one month; none carcinomatous.

16 mice painted two months; 3 carcinomatous.

13 mice painted three months; 9 carcinomatous.

12 mice painted four months; 12 carcinomatous.

The importance of continued application becomes apparent from this table."

The painted skins of 45 mice, living or dead, have been examined in section from which it appears that the hyperplasia begins very early but that without exception the infiltration commences only after at least four months of continued application of the tar. In exceptional cases of rapid development we must admit an individual predisposition. If the painting is continued only during four months when it ceases the deep infiltration is rare. Nevertheless, in the course of the following months the cancer fatally appears. Formations that are histologically benign may be, therefore, biologically malignant [See also Murray and Woglum] and only manifest their malignancy at a later date when the growth becomes invasive and destructive. Such growths are latent carcinomas. By the term latency he means the time that intervenes between the time when the painting has rendered the cells biologically malignant and the moment when the

invasive growth begins, the paintings having meanwhile been suspended.

Since mice painted during only one month escape cancer and those painted during four months invariably develop a malignant tumor, we may estimate the duration of the paintings necessary to produce this transformation of tissue at about two to three months. In most of these mice the development of the carcinoma is slower to appear than in those which have been painted four months. As a matter of fact, in the former it develops only eight or ten months after the beginning of the tar treatment while in the latter it manifests itself six or seven months after the beginning of the treatment. The longest time of latency he has observed was in a mouse which was tar painted for two months and died cancerous 317 days after the beginning of the paintings. Here the period of latency was about eight months. Inasmuch as mice painted four months or more show cancers after six or seven months (the longest time was 235 days) we must admit that the period of latency may be shortened by continuing the paintings after the biological transformation of the cells into malignant elements has taken place. The tumors can be obtained on very young mice with the same frequency and same rapidity of growth as on older mice. (*Comptes Rendus des Seances de la Société de Biologie, Paris, 22:754-757. July, 1922.*)

In a second paper read at the same time Bang states that the tar provokes an immediate intense proliferation of the epithelial cells so that the two layers of the normal epidermis give rise to several cellular layers. As determined by the examination of a great many sections in series the abnormal process takes place in the following order: thickening of the epithelium after one or two paintings; epithelial cysts about the tenth day; earliest formation of papillomas about the 29th day, but frequent only after two or three months, and visible to the naked eye only after four or five months; after this begins the epithelial invasion. In the course of the first month of paintings during which there is an epithelial thickening in full development no hyperplasia of the connective tissue is observed. Later this also takes place. After tar paintings continued for four months and more papillomas are always produced, which later are followed almost invariably by cancers.

The biological malignancy of the hyperplastic epithelium is accompanied ordinarily by a hyperplasia of the connective tissue.

All the processes are accompanied by inflammatory and hemorrhagic symptoms.

Some parts of the painted skin are more influenced than others.

In some cases the hyperplastic process tends to regress. In others it may persist to an advanced age without resulting in cancer.

"The decisive factor in the development of tar cancer is not, therefore, to be sought simply in the combined epithelial and connective tissue hyperplasias, not even when these hyperplasias end in the formation of papillomas visible to the naked eye. The hyperplastic processes are followed by carcinoma only in cases in which a more prolonged painting has given to them a biological malignancy." (I.c. pp. 757-759.)

Discussion.

Are the irritation tar cancers flatly contradictory of parasitism? Yamagiwa seems to think they are. I am less certain.

The tar treatments involve a long-continued open wound subject to and inviting all sorts of infections, so that if there were a cancer parasite in the environment of any of these animals, either in the soil, or in the litter, or on its food, or on its skin, or on the walls of the cage, or in the dust of the room, or on the hands of men handling the wounds, or in or on any of the common skin parasites of these animals, it would be more or less certain to find lodgment and a very favorable nidus in these irritated raw places. The general impression one gets from the tar cancer experiments, so far detailed, is that it requires great labor and patience to produce positive results, and these results, which cannot be denied but which may be interpreted in different ways, are fewer and less striking than one might expect if the tar itself is their sole cause. In the first Japanese experiments of Yamagiwa and Ichikawa papillomas were finally obtained in 32 out of 52 painted ears, but only 3 cases of infiltrating carcinoma were observed and no metastases (1916). In their additional experiments described in 1917 they report 8 cases of carcinoma from 45 experimental animals with 2 lymph node metastases, and 5 cases of "beginning carcinoma." White rabbits were least susceptible (1 case in 13) and black and gray-black rabbits, most susceptible (100 per cent), but only 3 animals were under treatment. For the animals as a whole and reckoning the 5 "beginning" cases with the 8 typical carcinomas we have 13 cases only from the 45 animals after treatment extending over many months.

In their 1918 paper (J. Cancer Research) they report use of 137 rabbit ears (four series) with production of seven complete carcinomas, 16 in an early stage and 8 in earliest stage.

In Tsutsui's experiments, as we have seen, he obtained 17 cancers in 259 mice, or in 67, excluding those which died before the 100th day.

The total of Fibiger's three series on mice is somewhat better, viz., 24 cases of carcinoma (or carcino-sarcoma) in 45 animals, and Bang's are still better, but mice, especially old mice, and mice of certain breeds, are much subject to cancers in the absence of tar painting. Possibly, therefore, some other cause may have been at work besides the tar treatment, e. g., some organism able to enter and infect a long continued open wound. Fibiger gives for his three series where the treatment was continued for 180 days, or longer, 24 cases out of 26 animals, and Bang 75 out of 77, which is all that one could ask, but Dr. Marsh and Miss Slye have both bred races of mice in which 100 per cent become cancerous as they get old, without any tar treatment, and Miss Slye tells me that these cancers often begin in accidental wounds. When from the tar we have a definite chemical substance by means of which cancers can be produced early in life in 100 per cent of cases, as can be done with crown-gall bacteria, then we may believe that cancer can be produced in the absence of parasites and we shall be one step farther advanced toward the solution of the vexed problem of its etiology. Parasites will not have been eliminated thereby in all cases, but we shall know definitely that any substance capable of acting on the cell in the same manner as the excretions of certain bacteria and of certain worms or their symbionts will bring about the same results.

Yamagiwa's additional experiments on the breasts of rabbits are still less conclusive: 31 coal tar injections into the breasts of 200 rabbits with only one cancer (a fibromyxosarcoma with metastases) at end of 23 months (M. a. d. Med. Fac. Univ. Tokyo, Dec. 28, 1920, 25, 2). Seedorff, who repeated this experiment on 39 rabbits, 8 of which survived one year of treatment, failed altogether (1922).

g. Swiss Experiments with Coal Tar Distillates

Recently an attempt has been made by Bloch and Dreifuss (Sch. Med. Wochenschr. Nov. 10, 1921) to isolate the active principle from coal tar and these efforts if we may believe the preliminary report have proved remarkably successful and will greatly advance our knowledge.

They began work in 1920 using rabbits, with the same results as Yamagiwa (number not stated); guinea pigs, which proved resistant; and white mice, which yielded results "exceeding anything hitherto obtained." Raw tar was used only on a small part of the animals. All the fine results were obtained with a definite fraction of the coal tar, produced by distillation. Corresponding to English observations on

the variable number of cancers in men who handle various kinds of coal tar products (H. C. Ross, J. Cancer Research, 1918) the bases, phenols and hydrocarbons, which come over at low temperatures, were found to be negligible. With the first two nothing was obtained and with the low-boiling hydro-carbons only mild results which first appeared after many days. On the contrary with a product which distills over above 300° C. and is soluble in benzol, astonishing results were obtained. With such a distillate they state that they were able to produce skin cancers on mice in four months' time in 100 per cent of the cases (number not stated nor strains or age of mice employed). Their technique was the same as that used by Yamagiwa. The substance used was painted on the back of the mouse toward the tail every other day for 160 days or more. After a variable time the treatment was discontinued. Except such animals as were killed early for study, the mice lived from 150 to 250 days after the beginning of the experiment, and a few lived longer, dying with signs of cachexia. Photographs of two mice shown were made on the 207th and on the 217th day.

The macroscopic clinical changes in the mice were as follows: After about five months, seldom earlier, tumors appeared here and there on the skin, which early lost its hair. They were at first only of pin-head size but grew rapidly. They often resembled flat warts, but soon became rounded with a broad base. The arched surface generally showed early a fine, rough-horny verrucosity. The number of these tumors varied greatly. On one mouse there were 22. Some of these tumors receded and others fell off, but most of them continued to grow. After a while the growth was much more rapid not only peripherally but also in the depths. Sometimes from the beginning superficial flat erosions appeared instead of raised tumors. Thus the development of the tumors was in two directions but there were mixtures of the two forms. One of these forms greatly resembled many basal cell carcinomas of the human skin. The other, which appears to have been the more common form, was characterized by the presence of horny masses which were sometimes several centimeters long. Under these hard, horny masses was a bleeding papillary ulcer. Most of these tumors, like the preceding, were surrounded by a thick, firm, pale, non-ulcerated edge. In spots in both forms there were strong inflammatory reactions and even pus.

The most important fact in connection with these tumors is that after the treatment ceased they continued to

grow both on the surface and in the depths. This further growth was sometimes very rapid, producing ulcerated and hyperkeratotic tumors several centimeters in diameter and in height.

These new formations destroyed the subcutaneous tissue, penetrated into the muscles and even through the wall of the peritoneum. When they lay near the backbone this was strongly twisted. In one case the bony tissue was also attacked and the tumor reached from the insert of the tail to far down on the thigh. Metastases were observed in the axillary and the inguinal glands. These glands were swollen, reddish, succulent and showed plainly the tumor tissue even to the naked eye and strikingly under the microscope. Still more frequent and interesting were metastases in the lungs. They appeared in various lobes in the form of conspicuous white, hard, red-bordered nodules from the size of a pin head to a pea. More than 20 such were seen in the lungs of a single animal and a microscopic examination showed that many more were present. These lung metastases were relatively frequent being found in 30 to 40 per cent of the older animals. The behavior of the connective tissue was inconstant. A definite relation of the epithelial proliferation to the grade of inflammation could not be made out. The principal changes were in the skin. The early stages were benign (gutartige) acanthoses and hyperkeratoses, but gradually or suddenly the picture changed to one of invasion and metastasis and epithelial pearls were very frequent in the invasive strands. For a time these tumors respect the muscles but then break through. The tumor is histologically a carcoid and resembles the type *carcinoma solidum*.

"Mit dieser Substanz konnten wir in relative kurzer Zeit (ca. 4 Monate) in 100% mächtige, ausserordentlich rasch wachsende und maligne Tumoren hervorrufen."

The authors publish good, convincing figures. The fractioning of the tar was done in conjunction with Dr. Labouchere and another paper is contemplated. They do not name the substance and perhaps have not yet determined it, but it must be one of the many associates of crude anthracene. Purified anthracene, judging from factory experience in England (O'Donovan) appears to be harmless, but among English factory workers in crude anthracene, keratoses are very common and they often end in cancers.

h. English Experiments with Extracts

(I) Dr. Murray says (Brit. M. J., Dec. 9, 1922):

"I have found that an extremely active extract can be prepared from tar by successive extractions with water, alcohol, and ether. The ethereal extract gave 50 per cent malignant growths in twelve months, reckoned on

the total number of animals that survived for four months."

(II) Dr. R. D. Passey, of Guy's Hospital, London, has also confirmed experimentally the production of malignant tumors by soot extracts (Brit. M. J., Dec. 9, 1922, p. 1112-1113). He tested three extracts of coal soot made as follows:

I. Simple, repeated ether extracts concentrated to a syrup. The water extract of this was faintly acid.

II. Three parts of soot and one part of quick lime intimately mixed, stirred into a thick paste with distilled water and spread on a glass plate in thin layers to dry. This mixture gave off ammonia freely. When dry it was broken up and repeatedly extracted with ether till the washings were a light sherry color. It was then filtered, the ether distilled off and the residue stored for use. The water extract of this was faintly alkaline. Neither I nor II were soluble to any great extent in water.

III. One part of II was added to 10 parts of N/10 HCl. and shaken thoroughly in a separating funnel. This washing was repeated with fresh additions of weak acid till the extract was nearly colorless. The bulky, strongly acid water extract was then filtered and rendered slightly alkaline with N/1 NaOH. This caused an oily yellowish precipitate. This was repeatedly extracted with ether which was then distilled off. The water extract of the residue was feebly alkaline.

Young adult, white mice were then painted repeatedly for a long time with each residue—20 with I, 40 with II and 20 with III. Applications were made along the back over an area 2 cm. by 5 mm. two or three times a week after removal of the hair by means of barium sulphide, the thick extracts being diluted with a minimum of ether for ease of application. Nos. I and III were found to be negligible. The former produced warts in only three animals by the end of six months and the latter in only one animal and neither caused definite malignant changes. On the contrary, II produced cancers. This substance which contained the basic and neutral ether soluble fraction was brown in color and of the consistency of very thick treacle.

The painting with II began Dec. 16, 1920, and the first wart appeared in ten weeks after 31 applications. By March 18, 1921, 16 mice had developed warts (the survivors at this date were 18) and at the end of the third month 50 per cent of the then surviving mice (number not stated) subsequently developed malignant tumors. The first case of malignancy was established microscopically June 12, 1921.

Subsequently two groups of mice of 50 each, as nearly identical in size and

color as possible, were painted with II, in the same manner, but were fed differently. One group (A) received a diet rich in fat-soluble vitamin A and the other group (B) a diet poor in fat-soluble vitamin A. The only visible difference was that the warts appeared a little earlier in B. Of the survivors at the end of the fifth month (number not stated) 42.3 per cent developed malignancy in A, and 47.3 per cent in B. Forms suggesting sarcomata also occurred, but were considered to be carcinomata.

"Malignancy was determined (1) where possible by autoplasty, as suggested by Dr. Murray; (2) by secondary deposits or recurrence after wide excision; or (3) by deep invasion of muscle where the animal had died before 1 and 2 had time to occur."

VI. ANILIN-DYE CANCERS

Various anilin compounds have been under suspicion for a number of years as the cause of bladder and other malignant human tumors. The first reported case was at least as far back as 1895.

a. Scarlet Red

In 1906 Bernhard Fischer reported on some remarkable results he had obtained by injecting rabbits' ears with olive oil saturated with scarlet red (Muenchen m. Wchnschr. Nr. 42). Under this treatment the epithelium began to grow, thicken and send down groups of invasive cells into the deeper tissues with development of abnormal mitoses, pronounced keratinization of the surface layers, and the formation of many epithelial pearls in the deeper invasive masses of the epithelium, quite after the manner of skin cancer. These results were obtained only by injection; they could not be obtained by painting the surface and the growths ceased when all the olive oil was absorbed.

Following Fischer's publication, which excited a good deal of interest, many persons repeated his experiments, but after some years there was a general consensus of opinion among oncologists that the epithelial proliferation, although remarkable in many ways, could not be considered as a cancer because it always receded soon after the treatments ceased. Here apparently, as in case of the coal-tar treatments, the failures were due to lack of persistency on the part of the experimenters, since in 1918 Yamagiwa and Ohno reported success with scarlet red dissolved in olive oil when injected into the wall of the ovary in hens (Gann, Bd. XII, S. 3). Their experiments began in December, 1914. They used 41 sound chicks or hens, injecting the fowls 1 to 5 times at intervals with a laparotomy in each case. They made 3 series of experiments—(1) 12 hens from which they obtained 1 case of multiple adenocarcinoma, (11) 9 hens, yielding 1 case of gland carcinoma with metas-

tases, (111) 20 hens from which they obtained 1 case of gland carcinoma with dissemination. I have read only the brief German abstract of their first Japanese paper (prepared, however, by Yamagiwa). To be entirely convincing this work should be repeated since the percentage of cases is small and perhaps not beyond the limits of error, although the authors believe it to be so.

b. Sudan III.

In 1918 (Gann, Vol. XII, parts 3 and 4) Dr. Nobumasa Umehara, professor of general pathology and pathological anatomy in the medical high school in Kyoto, added another link to the preceding chain of evidence.

He had obtained a knotty tumor, from the breast of a white rat, which structurally was an adenofibroma. This he was able to transplant to other white rats through 14 generations with a constant structure except that toward the end the connective tissue increased in amount and the gland tissue decreased correspondingly. The number of takes were also less toward the end. For these transplants he used 423 rats with 144 positive results. This tumor grew expansively to a large size but there were no metastases and there was no infiltration. Even when the tumor equaled or exceeded the weight of the rat there was no cachexia, but only nutritional disturbances ending in death.

Umehara then tried the effect of repeated injections into the tumor of the following substances: (1) 2% aethyl alcohol; (2) 1% cholesterol in olive oil; (3) 1% scarlet red in olive oil; and (4) 1% Sudan III in olive oil. The results with the first three substances were negative.

Of three rats injected with Sudan III one died after the eighth injection with no change in the nature of the tumor. Of the other two each of which received 17 injections, one lived until the 42nd day and the other until the 57th day. Both developed tumors as large as goose eggs. A part of each tumor repeated the well known adenofibroma structure but the rest and the major portion consisted of a gray-red translucent bloody mass with many necrotic spots. Under the microscope this part was sarcomatous, consisting of rapidly growing spindle cells, round cells and giant cells. Many mitoses were present. This sarcoma was transplanted through 14 generations. It grew expansively, invaded and metastasized, caused cachexia and killed. For these transplants 445 rats were used of which 291 gave positive results. No bacteria or other parasites were found in the sarcoma and injection of dead cells or the juice of the living cells did not cause the tumor. The tumor could not be transplanted to other experiment-

al animals nor easily into parti-colored rats (black and white).

CONCLUSIONS

What goes on inside a cancer cell that does not go on inside a normal cell? If we knew that we should be very near the solution of the cancer problem, and it is not beyond hope that eventually we shall know just that—chemically and structurally. We must conclude that the cell or its progenitors has been under a foreign stimulus of some sort. Everything we know about cancer points to this conclusion. In case of the crown-gall bacteria, acid and alkaline by-products are given off in simple culture media and we have a right to assume that they are also given off inside the plant where similar proteids and sugars are at their disposal. When applied to the surface of the plant these substances set up chemical and physical changes which lead to an excessive, disordered, hyperplasia growth and they probably do this in the tissues where they are produced by the parasite, but here our knowledge ends.

It may be that some element of the cell or of its environment which ordinarily acts as a break on cell division is destroyed or weakened by the action of certain physical and chemical activities (x-ray burns, common burns, arsenic, cobalt, tar products, products of worms and of bacteria) and so we get a cancer, that is, a cell-multiplication passing beyond physiological control.

The reason some worms cause tumors and others of the same origin (cat, cockroach) do not might be explained in at least any one of three ways: (1) The tumors that start first might absorb most of the nutriment and many other beginning cancers fail to develop for this reason. In many plants the buds which first develop exert an inhibiting influence on other buds. Destroy the former and then the latter will grow. (2) The individual larvae might excrete varying amounts of virus and the more virulent ones be those which cause the tumors (Fibiger's idea.) Some bacteria are known to be exceedingly variable in the amount of poison they produce and also some of the higher plants, e. g., digitalis. Why not also nematodes and tapeworms? (3) Some of the worms from the same individual (cat, cockroach), and this is the concept I have favored in this paper, might carry a living cancer germ (protozoan or bacterial) and others not, depending on the particular segment of the mother worm from which they originated. It is easily conceivable that some egg-laying segments of the mother worm and eggs from such segments might be infected and other segments and eggs not infected. Recently in the United States (J. Parasitology, March, 1922) Kudo and Heth-

erington have shown that a parasitic nematode (*Protosirura muris*) of the common house mouse harbors a protozoan in the epithelial cells of its intestine. This is a new species of microsporidian. Also in the Laboratory of Zoology and Comparative Anatomy in the University of Geneva, Switzerland, Guyenot, Naville and Ponse have found a microsporidian parasitic in the larvae of a Cestode living as a parasite in the sub-cutaneous conjunctive tissue, the muscles and the peritoneum of an adder (*Tropidonotus natrix* L.) coming from Italy. They find this microsporidian, which occurs with great frequency (89 per cent) is parasitic also in the tissues of the adder where it causes cellular reactions. (C. R. Soc. de Biologie, Paris, Seance du 22 juillet 1922, p. 635-637.)

One would think if the excessive growth were due only to a temporary depression of some function of the cell this would disappear and the malignant growth cease with the disappearance of the cause, just as normal growth ceases when the physiological stimulus is removed or counteracted, but if some growth-inhibiting element of the cell is permanently weakened or destroyed within certain cells then, just as we have bud-variation in animals and plants, unexplained as yet but reproducing itself, so we might have a disordered growth which would continue indefinitely in the descendants of such cells after the disappearance of the inciting cause, whatever that cause might be. This is Jensen's idea, and Fibiger's.

What is this inciting cause to a disordered growth? In some cases it seems to be an x-ray burn, the long continued action of soot, of coal tar, of paraffin, of anilin, of cobalt, of arsenic, etc. These are the irritants, it is not yet established that they are the actual cause. Moreover, when all is admitted, these are rare causes. For the ordinary forms of cancer, those seen every day by surgeons and x-ray men, there must be some other and more common cause, or causes. Some have said heredity does it, and certainly heredity plays its part, but I can think of inheritance only as preparing a suitable soil through the weakening of some of the protective forces of the body, and not as the direct cause of cancer any more than it is of tuberculosis. Mouse breeding experiments as ordinarily performed are incompetent to settle the question of the cause of cancer. They are carried on in crowded dirty quarters, almost always with an insufficient number of helpers, and they do not yield the effects of pure heredity, but of a bad inheritance plus the action of ecto- and endo-parasites—of swarms of mites,

and nematodes, bedbugs, fleas and what not crawling about and biting and burrowing from youth to age. Until mice can be bred free from what have now become very suspicious complications we shall never know what weight to give pure heredity. Why does not some one breed them clean? I think it would be quite possible to take the young from the mother at birth or just prior to birth and rear them under clean conditions free from parasites and have mice of cancerous lineage remain free from cancer. This is something that can be determined by direct experiment. It offers no insuperable difficulty so far as I can see and it is of immense importance. We bring up babies in incubators, why not mice?

The Cat-Taenia-Rat-Liver-Cyst-Sarcoma experiments at the Crocker Institute seem to put a quietus on the doctrine that heredity is the cause of cancer. They have now been able, the director tells me, to interbreed the sarcomatous rats so as to have strains 100 per cent of which are sarcomatous, but only if the tapeworm irritant is present. If it is not present, then the susceptibility to the sarcoma remains latent. Bang in Copenhagen also experimented with this disease some years ago and failed to get any positive results, undoubtedly because he was working with a resistant strain. Very fortunately, after the first failure at the Crocker Institute, the director decided to continue the experiments on other rats, some of which proved susceptible and have given the wonderful results already detailed.

A long continued physiologically wrong course of living, excessive eating and drinking, or chewing and smoking, for example, might also be regarded as preparing a suitable soil for cancer, but hardly as being the direct inciting cause. What occurs here may be the premature aging through excessive stimulation of some of the protective organs of the body enabling a weak parasite to attack and this might occur early in some persons and late in other persons, or never. We must certainly abandon the idea that carcinoma is only a disease of old persons. It is most common in the old but it occurs also sometimes in the young, quite frequently in the middle aged, and as we have seen can be produced in the youngest mice by tar painting. At any age, however, I believe carcinoma is only the last stage in a series of physical degenerations. Probably no one can have cancer who is not ripe for it. Here is a great field for fruitful study.

In the light of the cancer-resembling structures I have found in crown gall, a tumor due to a schizomycete; of the filterable virus Rous has found in three

chicken sarcomas; of the cockroach nematode Fibiger has proved to be the precursor of stomach cancer in the rat; of Kopsch's frog tumors due to angleworm nematodes; and of the cat tapeworm Borrel and others have found closely associated with the rat liver-cyst sarcoma and Bullock and Curtis have proved up experimentally on sensitive rats, which, however, in spite of their inheritance, do not develop the tumor in the absence of the worm, together with all the other similar but experimentally less well established cases of acarid, verminous and protozoan association in cancer of men and animals, I think we must predicate the products of parasites or symbionts as the probable cause of most cancers or at least of their initial stages. In some cases perhaps several organisms act together or one heightens the action of another, and some of these organisms or viruses, as Rous has shown, are filterable through Berkefeld bougies and are probably ultramicroscopic, at least in some of their stages.

Whatever we may think as to the cause of human cancer, it cannot be denied that the ability to produce cancer in plants by means of bacteria, in chickens by means of a filterable virus (Rous), in rats by means of a nematode (Fibiger), in rats by means of a tapeworm (Bullock and Curtis), and in rabbits and mice by means of tar (Yamagiwa, Tsutsui, Fibiger, and many others) have so much advanced our knowledge and have so simplified the problem that we may hope for its full solution, so far as regards many forms of cancer, in the not distant future. As I have frequently pointed out, the crown gall organism acts to produce a tumor not mechanically but through its excretions and there is nothing contradictory of my ideas in the fact that cancers may be produced by tar products or by excretions from tapeworms and nematodes. Only I must still believe that the bulk of the evidence we now have points to microparasites as the probable cause of sarcomas and carcinomas. Very curious and instructive in this connection is the fact that many coal tar paintings and many verminous irritations do not end in cancers, and in those which do, it is not the whole stimulated region that becomes cancerous, but only tiny scattered areas which begin to behave differently exactly as if they had become infected.

Opposed to this view is the fact that no one has isolated any microparasite from carcinoma and aside from the filterable virus in chicken sarcomas, the nature of which is unknown, the same is true of sarcoma. But these are only negations! They do not disturb me, as I have said repeatedly, because the par-

asites of tuberculosis, of leprosy, of syphilis, of malaria and of yellow fever remained undiscovered for many years. We were two years trying to isolate the parasite of crown gall yet it is a very simple operation. Think also of the many plainly contagious human diseases, the cause of which still remains uncertain, I need only mention dengue fever, scarlet fever, small-pox and the pandemic influenza; nor need the fact that cancer does not appear to be contagious bulk very largely against this view. Malaria is not directly transmitted from person to person and yet it is due to a parasite. Human carcinoma also may perhaps require an intermediate host and it almost certainly requires for its growth a special, defective bodily condition, either a bad inheritance or a long continued bad environment, or both acting together.

We must expect to continue to find animal and plant parasites with peculiar methods of propagation difficult to discover and to find parasites much smaller than any microorganisms now known to us. There are plant viruses, the particles of which are so small that an ordinary bacterium swimming among them would be almost like a whale among minnows, or a zeppelin among cockchafers. There is an immense leeway for living things between the size of the largest molecules and that of the smallest known organisms. There are many filterable virus diseases in plants and more are being discovered every year. The virus of the tomato streak is exceedingly infectious and sometimes kills in three or four weeks yet we have not been able to isolate any organism. The same is true of the tobacco mosaic and yet the least particle of the juice of a diseased tobacco plant will infect a healthy one, and some of the particles of this virus will pass through a filter with pores only $3/100$ micron in diameter (Duggar). We are far from having sounded all the depths of parasitism and of symbiosis in either plants or animals.

I say nothing here about the work of Ford Robertson, John W. Nuzum and others who are now experimenting on animals with bacteria isolated from malignant tumors because the positive results thus far published are too few to be of any value as evidence.

If the statements of Bloch and Dreifus are confirmed as to the isolation of a specific cancer-producing substance from coal tar, then the tar cancer ex-

periments will have greatly advanced our knowledge of the etiology of cancer because as soon as we know that keratinizing cancers can be produced with a definite chemical substance we shall begin to make experiments and to get positive results with various chemically (or physiologically) related substances, some of which undoubtedly will be found to be the products of parasites, or symbionts. Coal itself is the product of decay. The symbiotic action of organisms is an almost untouched field in medicine and yet it is one of the commonest and most striking things in Nature, witness the lichen. It is probable, as Ewing has pointed out, that cancer in the broad sense of the term, the way in which I use it, is a complex of diseases with unrelated origins, but certainly we should not expect as many parasites as there are forms, for I have produced in plants at least three forms with one organism, viz., a conjunctive tissue tumor with few vessels, the common form; one with many vessels; and a solid embryoma. We do not yet know positively that sarcomas and carcinomas are not the response of *unlike tissues to the same or similar causes*. The fact that in a series of mouse-tumor transplantations we may begin with adeno-carcinoma and finally obtain a pure sarcoma points to this conclusion, as does also the occasional appearance of sarcoma in the nematode carcinomas and in the tar cancers. As I stated in my textbook⁶ two years ago (p. 511), I regard cancer as a phenomenon of continually interrupted healing. What we have now to determine is whether continually interrupted healing is of itself sufficient, whatever the agent, to cause cancer or whether in some types of the disease, if not in all, the raw surface of the chronic ulcer is to be considered only as the nidus on which a cancer germ or virus may be engrafted. As to this we shall know much more in the near future. The first view is the obvious one but the obvious is often misleading and sometimes the unexpected and strange which no one will believe turns out to be true. We should at least be on our guard against unclean raw foods, especially salads; should see to it that all house vermin, rats, mice, roaches, bedbugs, etc., are destroyed promptly, and should have all sources of irritation removed as speedily as possible, surgically or otherwise. All the histologists should look for worms in or near primary can-

cers and in each case the whole tumor should be cut and searched.

Finally, the great fundamental advance of the twentieth century in cancer research is the fact that cancers (both sarcomas and carcinomas) have now been produced experimentally, and we have only to correlate our knowledge and extend it a little along the lines indicated to have a definite solution of the whole problem.

To summarize the subject in a few words: The cause of cancer, so far as we now understand it, may be defined as an irritation acting on an organ or organs unable to withstand it owing to a transmitted or an acquired weakness. Heredity alone cannot cause cancer, but irritation (parasitic and possibly also non-parasitic) plus heredity can and does cause it. No such conclusions could possibly have been drawn twenty years ago. They are the measure of the progress we have made.

Footnotes

1. In another room were exhibited photographs and photomicrographs illustrating various crown galls, and specimens showing dwarfing and death of plants due to early terminal-bud inoculations. Some of these are shown on the accompanying plates.

2. Our first papers definitely establishing the cause of the disease were published in 1907 (Science, N. S., 25:671; and Centralbl. f. Bakteriologie, 20:89, Part 2.)

3. Recently Riker in the United States and Robinson and Walkden in England have denied this, maintaining that the organism is always between the cells (Phytopathology, 12:55; Annals of Botany, 37:299) and the subject is still in dispute.

4. In December Dr. Francis Carter Wood, Director of the Institute, told me that the count had reached to more than 700 cases and as this paper goes to press the total number of the cases exceeds 900.

5. W. Caspari has recently announced that autolyzed nematode eggs or *Taenia* larvae when injected into experimental animals will start sluggish tumors into a rapid growth, which he likens to taking off the brakes from a down-grade trolley (Ztschr. f. Krebsforsch. 1922).

6. An Introduction to Bacterial Diseases of Plants. W. B. Saunders Co., Philadelphia and London, 1920.

The Relative Value of Unfiltered Radium Emanation in Deep Therapy*

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IN REVIEWING the recent advances of physical therapy, one of the outstanding features has been the effort to determine dosage more accurately. This has undoubtedly been stimulated by the wave of enthusiasm over high-voltage x-rays. While the present methods of standardization by ionization may be open to criticism and subsequent change, they at least furnish a reasonable basis for calculation and comparison of different types of radiant energy.

It is not the purpose of this communication to discuss details of the various methods of applying physical agents. The object is rather to present in as practical a manner as possible the value of interstitial radiation and to compare it, briefly, with the different forms of external radiation.

When we speak of interstitial radiation at the Memorial Hospital, we refer to implantation, within the tissues, of unfiltered tubes of radium emanation. For the purpose of broadening the field to include those using needles containing radium element, the calculations to be shown later have been based on gamma radiation only.

Unfiltered radium emanation tubes, or, as we usually term them, "bare tubes," are fine glass capillary tubes 0.3 by 3 mm. in size, and prepared in such concentration that each tube contains from 0.5 mc. to 2 mc. of emanation. For most types of work about 1 mc. per tube has proved to be the most suitable amount. In some very bulky tumors stronger tubes may be used, and, likewise, in very small lesions or in delicate locations, such as near large blood vessels or nerves, tubes of 0.5 mc. or less are most applicable. These tubes can be readily sterilized by boiling, and Bagg has shown that the emanation is sufficiently bactericidal to sterilize the inside of the tube. This makes their use safe from a surgical viewpoint, even though a tube may be broken within the tissues. These small tubes are placed in the ends of hollow trocar needles, inserted within the tumor to the desired depth and then expelled by pressing in the trocar of the needle. Since radium emanation decreases in

value at the rate of approximately 15 per cent per day, it will be seen that the total radiation to be derived from a given tube can be calculated, if its original strength is known. One mc. of radium emanation buried interstitially and left in place gives a total radiation equivalent to 132 mc. hrs. It will also be seen that since the emanation decreases in value at only about 15 per cent per day, a continuous radiation is kept up over a period of many days. The advantages of such a method are at once apparent. It permits of uniform distribution of radiant energy throughout the desired area, whereas external radiation usually delivers its greatest intensity at the least vital part of the tumor—its surface rather than the actively infiltrating base. In addition

to accuracy, the intimacy of application has in our experience been one of the chief factors of success in all phases of treatment with physical agents. Unfortunately, we do not know as yet the relative values of beta and gamma radiation, but it is a significant fact that almost invariably our most brilliant results have been those in which beta radiation has played a conspicuous part.

By virtue of the uniformity of distribution possible in interstitial radiation, a smaller total amount of radiant energy is necessary than with external radiation, and less damage is done to skin and adjacent vital structures. The fact that radiation is prolonged over a period of several days permits of greater proportionate dosage.

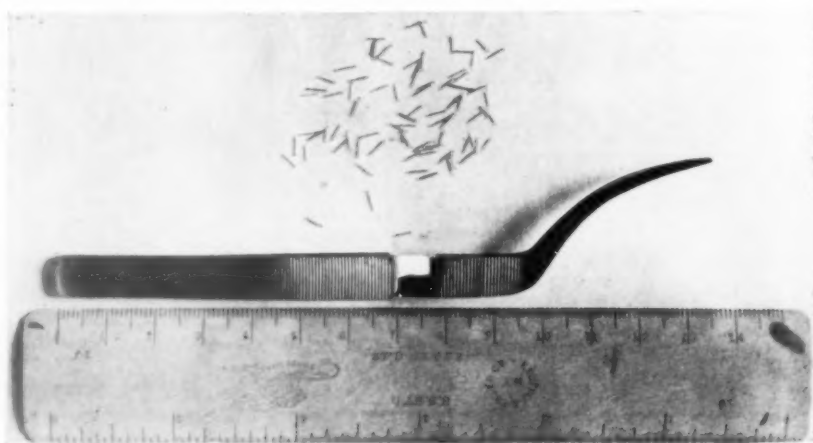


Fig. 1—Unfiltered radium emanation tubes for interstitial implantation.

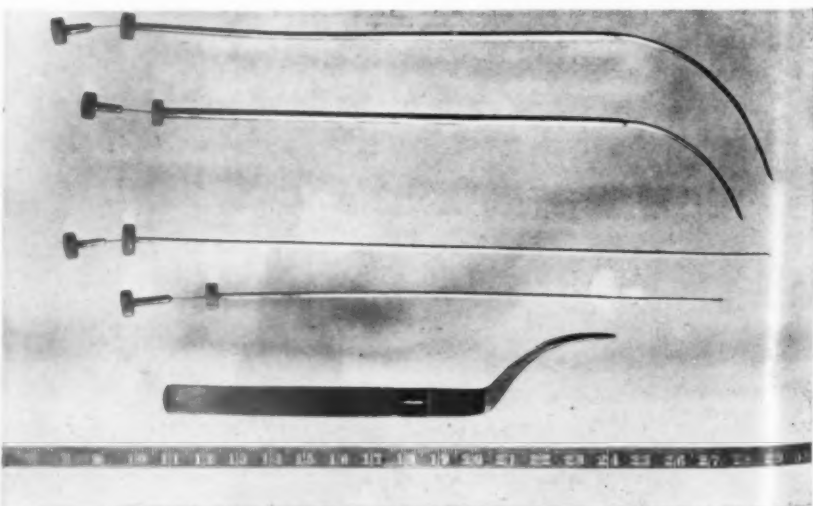


Fig. 2—Trocar needles for implanting radium emanation tubes.

*—Read at the Annual Meeting of the Radiological Society of North America, Detroit, Dec. 5, 1922.

UNFILTERED RADIUM EMANATION IN DEEP THERAPY—QUICK

X-ray factors: 200 kv., large fields, $\frac{1}{2}$ mm. Cu + $\frac{1}{2}$ mm. Al filter, dose at 70 cm. = 640 ma. min., at 50 cm. = 320 ma. min.

SCALE $\frac{1}{2}$

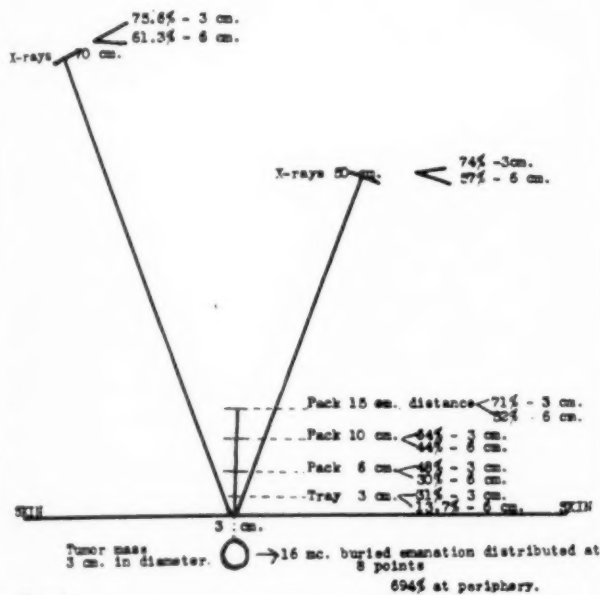


Fig. 3

Fig. 3—Diagram showing relative value of buried radium emanation, filtered radium externally, and high voltage x-rays. Percentages are in terms of erythema dose at skin surface taken as 100. Unfiltered radium emanation doses calculated for γ -rays only. Radium factors: filter, 2 mm. brass throughout; pack dose at 15 cm. = 42,000 mc. hrs; at 10 cm. = 20,000 mc. hrs; at 6 cm. = 10,000 mc. hrs. Tray dose at 3 cm. = 2200 mc. hrs.

X-ray factors: 200 kv., large fields, $\frac{1}{2}$ mm. Cu + $\frac{1}{2}$ mm. Al filter, dose at 70 cm. = 640 ma. min., at 50 cm. = 320 ma. min.

SCALE $\frac{1}{2}$

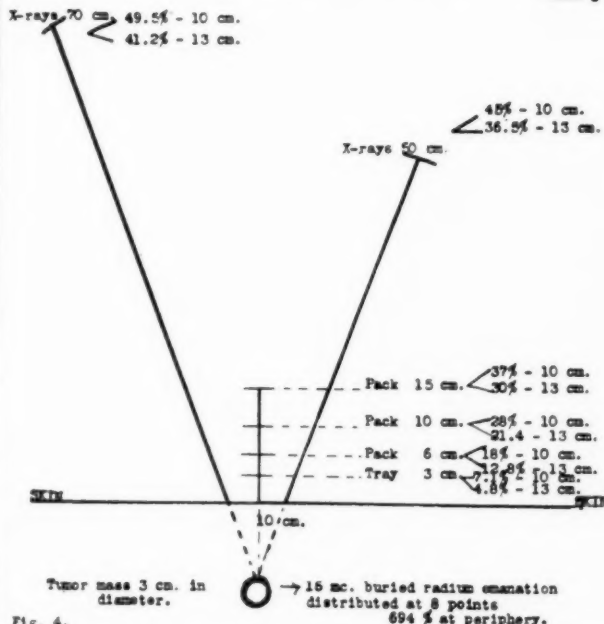


Fig. 4

Fig. 4—Diagram showing relative value of buried radium emanation, filtered radium externally, and high voltage x-rays. Percentages are in terms of erythema dose at skin surface taken as 100. Unfiltered radium emanation doses calculated for γ -rays only. Radium factors: filter, 2 mm. brass throughout; pack dose at 15 cm. = 42,000 mc. hrs; at 10 cm. = 20,000 mc. hrs; at 6 cm. = 10,000 mc. hrs. Tray dose at 3 cm. = 2200 mc. hrs.

X-ray factors: 200 kv., large fields, $\frac{1}{2}$ mm. Cu + $\frac{1}{2}$ mm. Al filter, dose at 70 cm. = 640 ma. min.; at 50 cm. = 320 ma. min.

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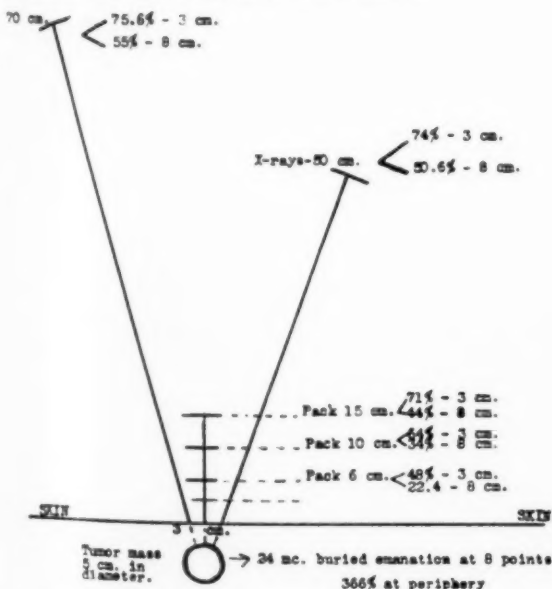


Fig. 5

Fig. 5—Diagram showing relative value of buried radium emanation, filtered radium externally, and high voltage x-rays. Percentages are in terms of erythema dose at skin surface taken as 100. Unfiltered radium emanation doses calculated for γ -rays only. Radium factors: filter, 2 mm. brass throughout; pack dose at 15 cm. = 42,000 mc. hrs; at 10 cm. = 20,000 mc. hrs; at 6 cm. = 10,000 mc. hrs. Tray dose at 3 cm. = 2200 mc. hrs.

X-ray factors: 200 kv., large fields, $\frac{1}{2}$ mm. Cu + $\frac{1}{2}$ mm. Al filter, at 70 cm. = 640 ma. min. at 50 cm. = 320 ma. min.

SCALE $\frac{1}{2}$

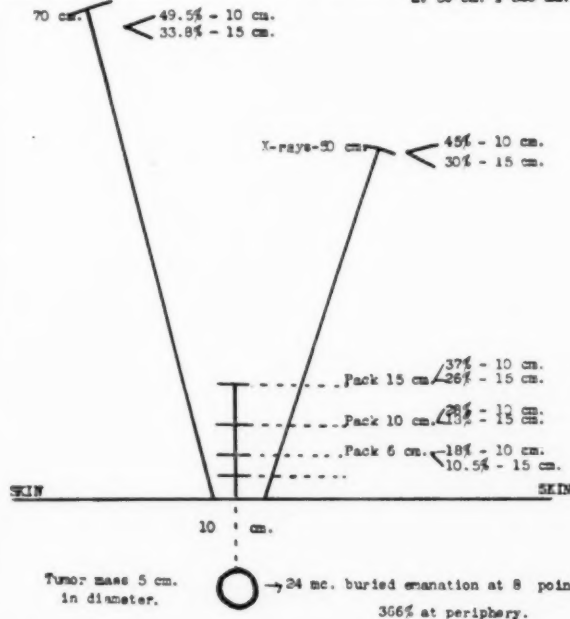


Fig. 6

Fig. 6—Diagram showing relative value of buried radium emanation, filtered radium externally, and high voltage x-rays. Percentages are in terms of erythema dose at skin surface taken as 100. Unfiltered radium emanation doses calculated for γ -rays only. Radium factors: filter, 2 mm. brass throughout; pack dose at 15 cm. = 42,000 mc. hrs; at 10 cm. = 20,000 mc. hrs; at 6 cm. = 10,000 mc. hrs. Tray dose at 3 cm. = 2200 mc. hrs.

UNFILTERED RADIUM EMANATION IN DEEP THERAPY—QUICK

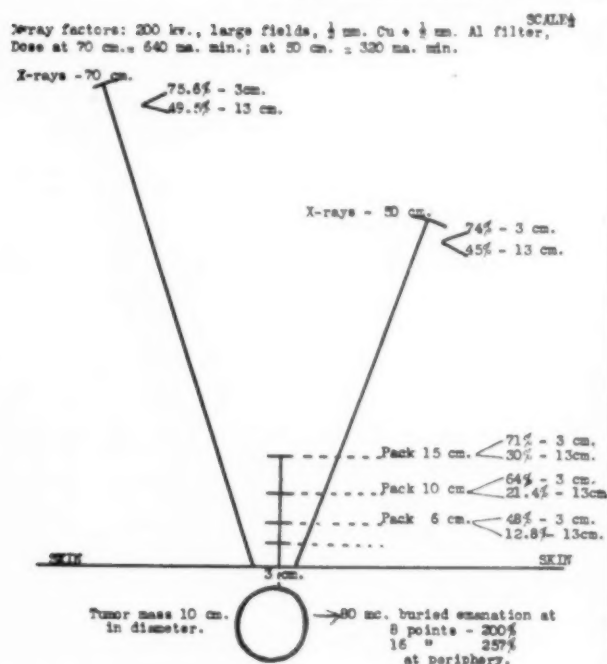


Fig. 7.

Fig. 7—Diagram showing relative value of buried radium emanation, filtered radium externally, and high voltage x-rays. Percentages are in terms of erythema dose at skin surface taken as 100. Unfiltered radium emanation doses calculated for γ -rays only. Radium factors: filter, 2 mm. brass throughout; pack dose at 15 cm. = 42,000 mc. hrs; at 10 cm. = 20,000 mc. hrs; at 6 cm. = 10,000 mc. hrs. Tray dose at 3 cm. = 2200 mc. hrs.

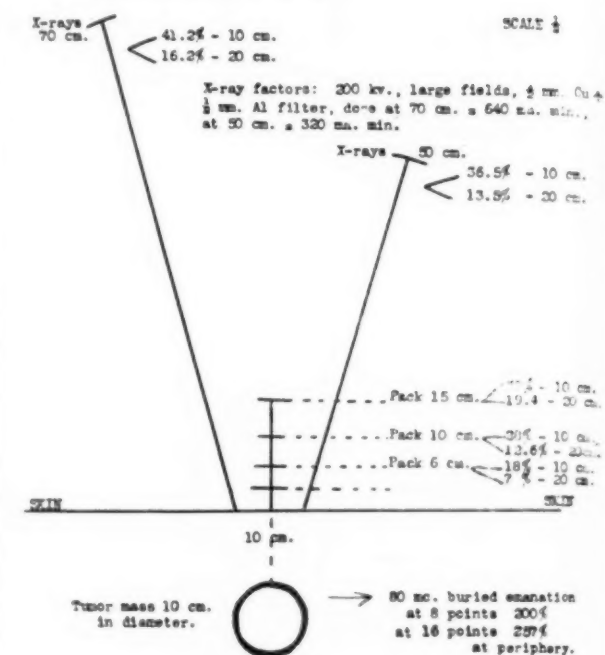


Fig. 8.

Fig. 8—Diagram showing relative value of buried radium emanation, filtered radium externally, and high voltage x-rays. Percentages are in terms of erythema dose at skin surface taken as 100. Unfiltered radium emanation doses calculated for γ -rays only. Radium factors: filter, 2 mm. brass throughout; pack dose at 15 cm. = 42,000 mc. hrs; at 10 cm. = 20,000 mc. hrs; at 6 cm. = 10,000 mc. hrs. Tray dose at 3 cm. = 2200 mc. hrs.

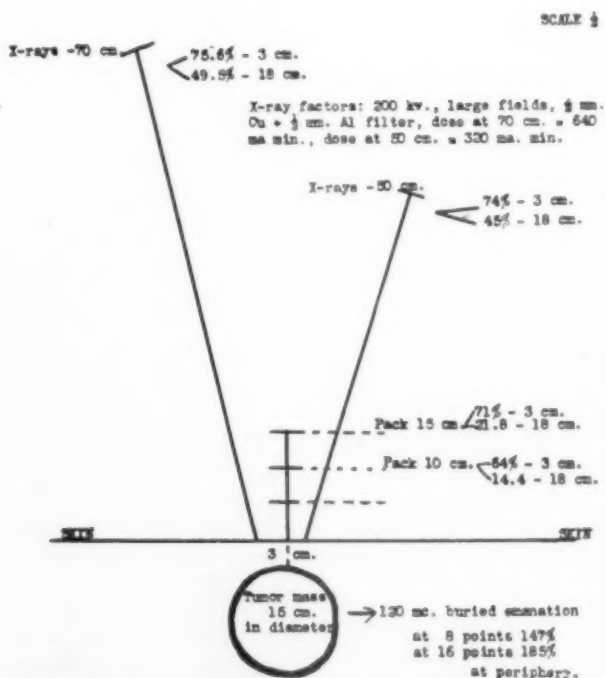


Fig. 9.

Fig. 9—Diagram showing relative value of buried radium emanation, filtered radium externally, and high voltage x-rays. Percentages are in terms of erythema dose at skin surface taken as 100. Unfiltered radium emanation doses calculated for γ -rays only. Radium factors: filter, 2 mm. brass throughout; pack dose at 15 cm. = 42,000 mc. hrs; at 10 cm. = 20,000 mc. hrs; at 6 cm. = 10,000 mc. hrs. Tray dose at 3 cm. = 2200 mc. hrs.

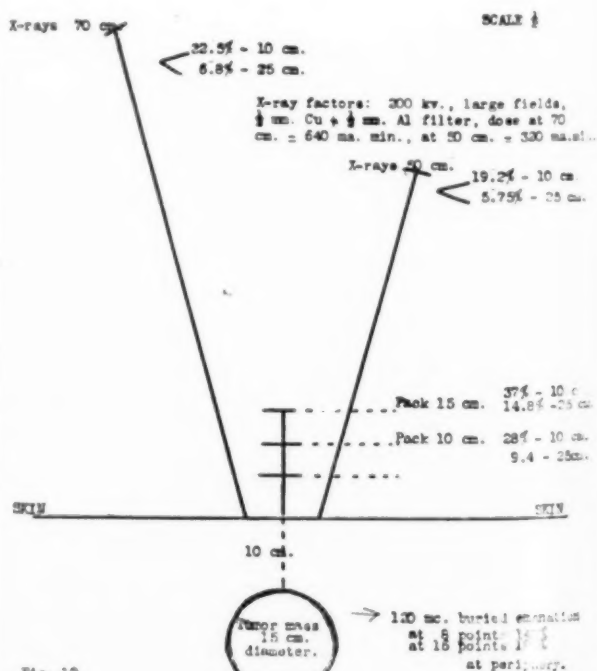


Fig. 10.

Fig. 10—Diagram showing relative value of buried radium emanation, filtered radium externally, and high voltage x-rays. Percentages are in terms of erythema dose at skin surface taken as 100. Unfiltered radium emanation doses calculated for γ -rays only. Radium factors: filter, 2 mm. brass throughout; pack dose at 15 cm. = 42,000 mc. hrs; at 10 cm. = 20,000 mc. hrs; at 6 cm. = 10,000 mc. hrs. Tray dose at 3 cm. = 2200 mc. hrs.

UNFILTERED RADIUM EMANATION IN DEEP THERAPY—QUICK

As a rule, an effort is made in using this method to accomplish a complete regression by a single dose. The advantages are two-fold. The bulk of the tumor is influenced by the radiation before the formation of new connective tissue has reached such proportions as to protect neoplastic cells. The procedure is less trying for the patient, and, while the local effect is more intense, the constitutional reactions are much less marked.

The flexibility of the method offers many interesting possibilities. The tubes may be buried in locations where surface applications cannot be retained accurately in place. The combinations with surgery are many. A tumor may be given an overdose of radiation with bare tubes and then be removed surgically at a later date when it is a much safer operative risk. This obtains with many bulky extensively ulcerated lesions where a prompt relief from absorption is essential to the patient's general health. Bare tubes may be inserted at any suspicious point in the base of a surgical field and the wound closed without endangering its healing. We make extensive use of this plan in our neck surgery. Many tumors considered operable are found at the time of exposure to be inoperable—bare tubes may here be utilized to advantage before the wound is closed. If there is any doubt as to the accuracy of placing the tubes, surgical exposure should be employed. The possibilities of this combination of surgery and bare tubes in dealing with intra-abdominal new growths are too numerous to mention.

The method, of course, has limitations. It is essentially one for use in dealing with localized growths. Danger from the glass tubes as foreign bodies is practically negligible. The intense local effect excites an inflammatory reaction which results ultimately in the encapsulation of the tube by fibrous tissue. There is danger of spreading infection deeper into the tissues if the tubes are introduced through foul ulcerating surfaces—under such circumstances care should be taken to introduce them through surrounding healthy tissues and directed toward the tumor base. The dangers of damage to nerves and blood vessels and of creating too much local caustic effect are not serious and are matters readily avoided by experience.

For the purpose of comparing, from a physical standpoint, the efficiency of bare tubes, within their field, with methods of external radiation, I have constructed a number of practical diagrams, giving in each instance the doses commonly used. The doses given for x-rays and external radium applica-

tions are those found by both experience and physical calculation to be the most efficient for the given distances. The doses given for bare tubes are those which we have found to be safe and

practical in our every day work. In the case of the larger tumors, especially, the doses given are decidedly minimum.

I am indebted to *Dr. Giocchino Failla*, the director of our physical



Fig. 11—Drawings to show method of implanting radium in neck as final stage of a surgical dissection.



Fig. 12—Osteogenic sarcoma of radius.



Fig. 13—Same tumor as shown in Fig. 12. Twenty-two months after implantation of radium emanation. Note contraction and deposit of new bone.

laboratories, for all of the percentages and calculations used in these comparisons.

A study of the diagrams will readily show the superiority of interstitial radiation. The figures given for bare tubes consider only gamma radiation and do not take in the tremendous local effects of beta rays. The number of point sources are far below those used in actual practice and hence indicate a lower dosage than is actually the case. In making the comparison with external radiation we must remember that these doses may be directed from two, three or four angles at the tumor. Even at that, the interstitial dose of gamma rays alone is superior to the multiple external cross-fire. The most marked advantage of interstitial over external radiation, of course, is in the smaller mass at greater depth.



Fig. 14—Squamous carcinoma of cheek.



Fig. 15—Same case as Fig. 14. One year after implantation of radium emanation plus external filtered radium.



Fig. 16—Angioma of tongue.



Fig. 17—Same case of Fig. 16. One year after buried radium emanation.



Fig. 18—Microphotograph to show lymphocytic infiltration round about an area treated by buried radium emanation.

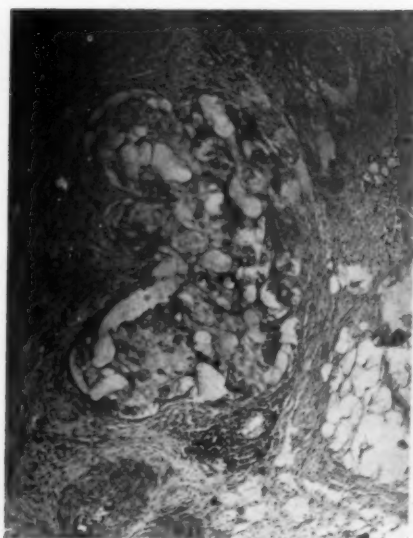


Fig. 19—Microphotograph of adenocarcinoma of rectum. Note lymphocytic infiltration and formation of new connective tissue.

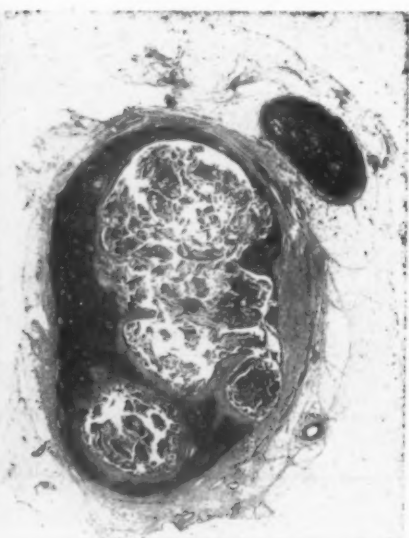


Fig. 20—Metastatic cervical node, squamous carcinoma. Six weeks after treatment by buried radium emanation. Note complete destruction of neoplastic tissue.

From a biological standpoint we now have ample evidence to indicate that the physical agents intensify the natural reaction of the tissues to new growth. In addition to the powerful destructive effect on tumor tissue itself, radiation tends to increase the exudation of lymphocytes and plasma cells and the growth of connective tissue around the tumor.

From a practical standpoint, as indicated by the accompanying microphotographs and six and a half years clinical experience with bare tubes, we are convinced that interstitial radiation intensifies these natural reactions to a far greater extent, with less damage to the patient, than does external radiation.

We are further convinced that bare tubes, both by reason of their flexibility in range of application and the added advantage of beta radiation, are superior to metal needles containing radium element for interstitial use.

The Routine X-Ray Examination of the Nasal Sinuses by Four Projections*

EDWARD S. BLAINE, M. D.
Chicago

THE USUAL technique in x-ray examination of the nasal sinuses consists of two exposures, one of which is a postero-anterior projection and the other is a lateral view. Inquiry among a large number of roentgenologists discloses this two projection method to be the rule. The anatomical situations of the several nasal sinuses are such that these two particular projections do not give the maximum diagnostic shadow value as to the pathological or non-pathological condition of all the four sinuses. With the usual postero-anterior, 23° projection, the shadows are of greatest value for the frontal sinuses but are of least value as to the sphenoid cells, with the ethmoid and maxillary sinuses falling, respectively, second and third in order. Notwithstanding this established fact, many specialists on nasal sinus diseases refer patients to the roentgenologist with a request for "one, postero-anterior view only." Many of them seem to be of the opinion that this view only is necessary in the detection of sinus pathology and that other projections are of no value and therefore superfluous and they feel that

they are saving the patient some of the usual fee because of the single exposure. The writer's experience teaches that this idea is incorrect. It seems to be the result of noting that the standard 23° projection really gives no satisfactory or reliable information other than an index to the condition of the frontal and ethmoid cells and occasionally the maxillary sinuses. This single exposure examination of the sinuses should be condemned as incomplete work and the roentgenologist who is satisfied with such a technique is remiss in his duty to himself, the patient and the referring specialist.

To those who use the 23° postero-anterior and the straight lateral projections it can be said that the greatest amount of information in these cases is obtained by adding two more exposures to those just enumerated. These are (a) the maxillary and (b) the sphenoid projections, the routine use of all four of which is advised. Specific reasons for the employment of each of these follows with their value over the usual two film exposure technique.

From a practical standpoint the twenty-three degree position of sinus study should be used mainly for the frontal and ethmoid cells because the maxillary sinuses are, in this projection,

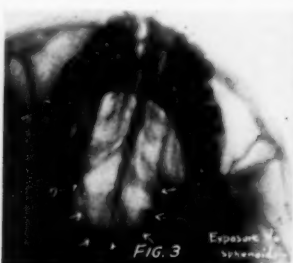
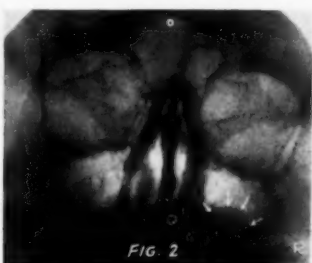
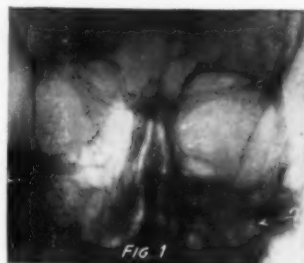
over-shadowed by the heavier portions of the temporal bones as well as those of the base of skull, while the sphenoid cells fall into the upper nasal areas, being easily confused therewith. It is not often that the cells, walls and inter-cellular septum of the sphenoids can be identified on this particular exposure.

To enhance the diagnostic value of x-ray studies of the nasal sinuses the following four projections are recommended: the 23°, postero-anterior; the maxillary, postero-anterior; the sphenoid, superior-inferior; the lateral.

None of these four projections is a new one and all have received extended attention in x-ray literature for a long time, but the routine use of all of them is seldom found to be the practice, the first and fourth being the rule in most laboratories. There are a few roentgenologists who do use routinely three of these positions and a still smaller number whom I have found using all four projections.

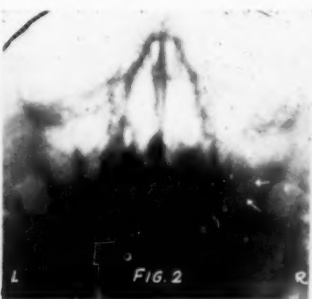
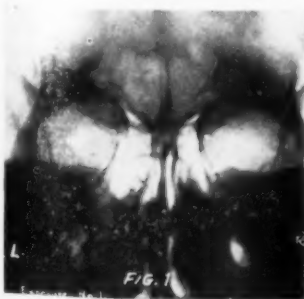
FIRST PROJECTION

The value of the twenty-three degree projection is known to all acquainted with this work and needs no extended elaboration in this presentation. The film holder or cassette is placed so that its upper edge is lifted away from the surface of the table,



Case I.—**Fig. 1**—Frontal-ethmoid: (23°) projection, postero-anterior: frontal asymmetrical, both clear; ethmoids, left clear, right diseased (note unsatisfactory shadows of antra). **Fig. 2**—Maxillary projection: postero-anterior (Water's position): left clear, right has rounded tumor, probably polyp or mucous (not visualized on 23° projection). Frontal shadows

confirmed. **Fig. 3**—Vertical sphenoid projection: superior-inferior, showing clear sphenoid cells, fairly symmetrical outline and extent (not seen on 23° projection). **Fig. 4**—Lateral projection revealing topography of all sinuses, particularly the frontal and sphenoid areas.



Case II.—**Fig. 1**—Frontal-ethmoid: postero-anterior projection, large frontals, irregular configuration, right cell faintly clouded; ethmoids, right-side cells are slightly less transparent than left; the side is clear. **Fig. 2**—Maxillary: postero-anterior projection, left antrum lacks transparency in lower two-thirds, probably thickened membrane; right antrum con-

tains rounded shadow lying against nasal wall, probably a mucous (not demonstrated on exposure No. 1). **Fig. 3**—Sphenoid: superior-inferior projection, asymmetry of cells, very large left, small right, clouding on left. **Fig. 4**—Lateral projection: deep frontal, shallow sphenoid.

ROUTINE X-RAY EXAMINATION OF NASAL SINUSES—BLAINE

resting on a support which is approximately 23° with horizontal; the patient lies prone with the forehead against the film holder and with the nose flattened against its surface; the x-ray tube is directed vertically downward with central axis of x-ray emerging at the glabella. The resulting shadows are the very best possible of the frontal and ethmoid cells. This projection should be used in determining the condition of the frontal and ethmoid sinuses only. The frontal sinuses are studied to determine the topography, symmetry, extent on each side of the median line, extent upwards into the frontal bone, size of the horizontal recess, presence or absence of bilateral or unilateral double cell formation, complete or incomplete septa, absence of frontal cells on one or both sides, transparency, translucency or opacity of one cell as compared with the other, and other variants from the normal. The shadows of the ethmoid cells are noted to determine their extent, transparency, translucency or opacity to the x-ray. They lie below the frontal sinuses and between the outer nasal and inner orbital walls, and are above the maxillary sinus shadows, sometimes overlapping these boundaries. They are normally quite transparent to the x-ray. When in normal condition both ethmoid groups are of an equal degree of clear shadow. The presence of pus or other products of inflammation reduces the transparency in proportion to the amount of increase of such products.

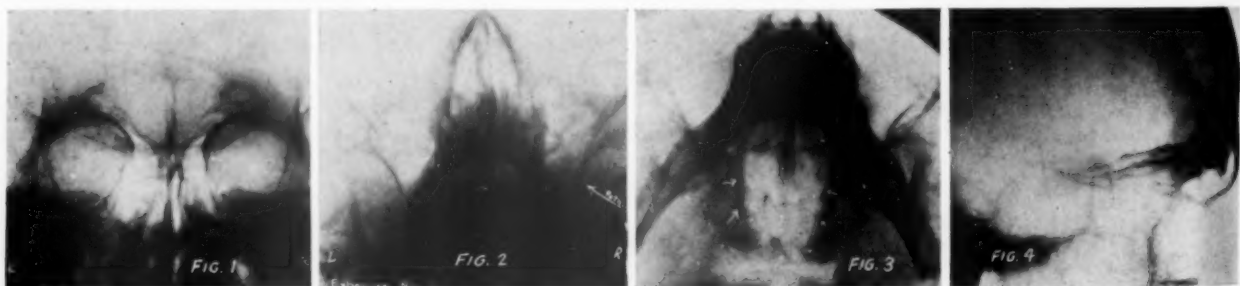
SECOND PROJECTION

The maxillary projection, often referred to as the "Waters position," is of greatest value in determining the condition of the antra. The film holder or cassette lies in horizontal position, preferably four and one-half inches above the table surface, the patient lies prone with tip of chin resting on the film holder and tip of nose barely in contact with its surface; the central axis of x-ray is directed so that it passes vertically downward through the skull, emerging at the tip of the nose. This position results in tilting the head backward which causes the temporal bone shadows to fall below the lowest margin of the maxillary sinuses. Thus, both normal antra are seen as clear uncovered triangular areas with rounded corners lying on both sides of the nasal passages. With this projection a far greater positiveness is obtained in reading the shadows than is possible with the first projection. The frontal sinuses are seen to be larger than they are seen on the first exposure, due to their greater distance from the film, but a check up on the shadow densities of 23° exposure is easily made. The ethmoid sinuses are blocked out by the shadows of the nasal bones. In determining the presence or absence of pathological change in the maxillary sinuses one finds it possible to discover on this exposure very slight shadow variations and often lesions not detected on the 23° projection. Then, too, doubtful translucencies on the 23° plate

are identified as a positive or negative finding, as the case may be. It is the one means of demonstrating polyps and similar tumors in the antrum. (In cases where a diffuse even density of marked degree is found it is advisable to make a supplementary exposure with patient's head in upright position, directing the x-ray horizontally through the back of head. This will reveal whether a fluid level is present, thus distinguishing between a greatly thickened membrane lining the antrum, or other non-fluid condition, from pus or other free fluid in the antrum.)

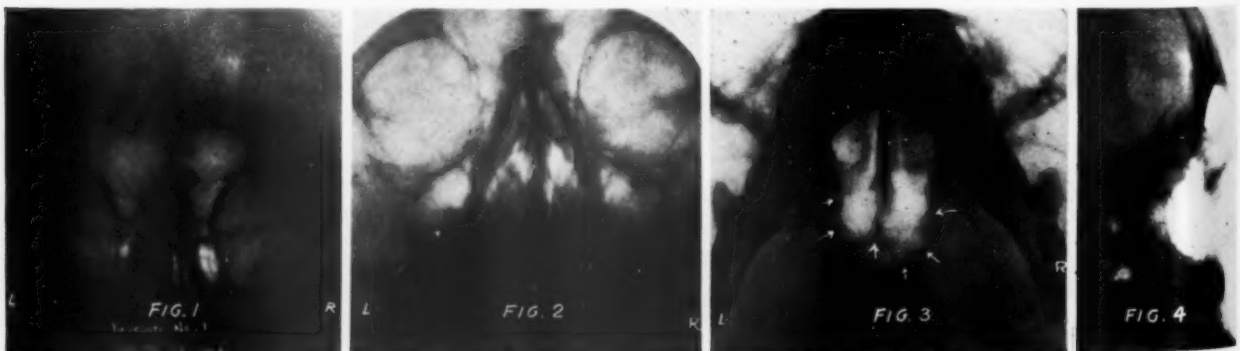
THIRD PROJECTION

The sphenoid cells lie on both sides of the median line in the body of the sphenoid bone which is practically in the center of the base of the skull. They are usually separated by a thin bony wall or septum. Occasionally these cells can be identified on the twenty-three degree postero-anterior projection, but this occurs so seldom that this exposure cannot be depended upon when there is a question of disease. Several methods of examination of the sphenoid cells have been proposed and used by various roentgenologists, some projecting the cells into the orbits (Pfahler), some using other technique, but the most practical one is the superior-inferior projection as advised by Law. The plate is placed in horizontal position, preferably about four and one-half inches higher than the table on which the patient lies prone. The chin is extended to its maximum and the inferior



Case III.—**Fig. 1**—Frontal-ethmoid: postero-anterior projection, frontals large size, cloudy right, clear left; ethmoids, less clear right, normal left. **Fig. 2**—Maxillary: postero-anterior projection; left antrum is clear, right antrum cloudy.

Fig. 3—Sphenoid: superior-inferior projection, both cells large (occupying all of body of sphenoid), symmetrical and clear. (Also confirmation of right antrum pathology.) **Fig. 4**—Lateral projection: frontals not very deep, large sphenoids.



Case IV.—**Fig. 1**—Frontal-ethmoid: postero-anterior, a projection, frontal cells medium size, fairly symmetrical, both of normal transparency. The intercellular bony septum is markedly widened (nonpathological) in lower portion encroaching on both cells. Ethmoids on left are considerably less transparent than normal, on right are clear. **Fig. 2**—

Maxillary: postero-anterior projection, both cells distinctly clouded in lower portions, suggesting marked thickening of mucous membrane lining the floor and extending upwards on walls as from old chronic inflammation. **Fig. 3**—Sphenoid: superior-inferior projection, left cell smaller than right, both clear. **Fig. 4**—Lateral projection: frontals of normal depth, sphenoids (cut off on illustration) are large.

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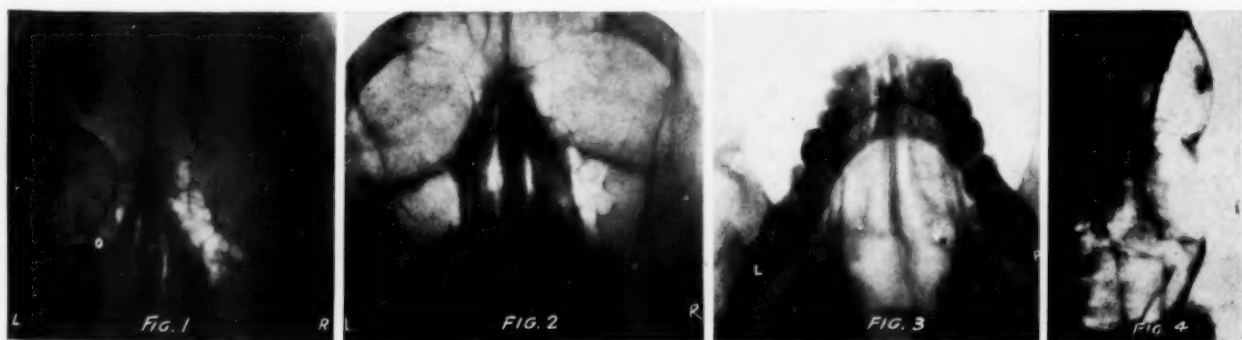
margins of the jaws lie parallel and directly in contact with the surface of the film holder. The near edge of the film holder or cassette rests against the episternal notch, care being used that the patient's breathing be not interfered with by pressure on the trachea, which in this position is forced against the edges of the cassette. The central axis of the x-ray beam is directed vertically downward through the vertex of the head to emerge at a point which is on a line with the angles of the lower jaw. This projection throws both sphenoid cells into the center of the film and the sphenoid area is found just posterior to (often overlapping) the posterior nares. The shadow outlines of both sinuses can usually be readily identified lying immediately in front of the less dense shadow of the pharynx. A patient of short stature and individuals with a short neck cannot extend the head sufficiently to obtain the required position; in this event the x-ray tube is moved towards the top of the table and is tilted backwards at such an angle as will permit the central axis of the x-ray beam to pass through the vertex of the skull, through a point midway between the external angular process of the orbit and the canal of the ear, and emerging at the angle of the jaw. The shadows of the sphenoid sinuses reveal the size, shape, symmetry and condition as to transparency, translucency or opacity to the passage of the x-rays. On this projection it is surprising to find the frequently differ-

ent sizes of right and left sinuses, and in a few instances the writer has found a single cell instead of the usual bilateral cavities, no dividing septum being present. In two cases a total absence of sphenoid sinuses, diagnosed clinically as being infected, has been determined by this method. Obviously, a cloudy or opaque cell on one side will present a marked contrast to an opposite one if it is of a normal transparency. On this projection the anterior and posterior clinoid processes may be visualized and the hyoid bone, which is of more or less horseshoe shape, is also seen. In addition one observes the anterior arch of the atlas (first cervical vertebra) and the odontoid process of the axis (second cervical vertebra) at the lower edge of the film. The temporo-mandibular articulations, rami and body of the mandible are seen in this direct superior-inferior view. In some cases large inferior turbinate bones will overlie the anterior portions of the sphenoid cells and one must, of course, discount such shadows and not mistake them for evidence of sinus disease. On this projection, too, it often happens that a check up on the radiability of the frontal and maxillary cells can be made to further substantiate variations in transparency found on the first two projections, thus adding to its value.

FOURTH PROJECTION

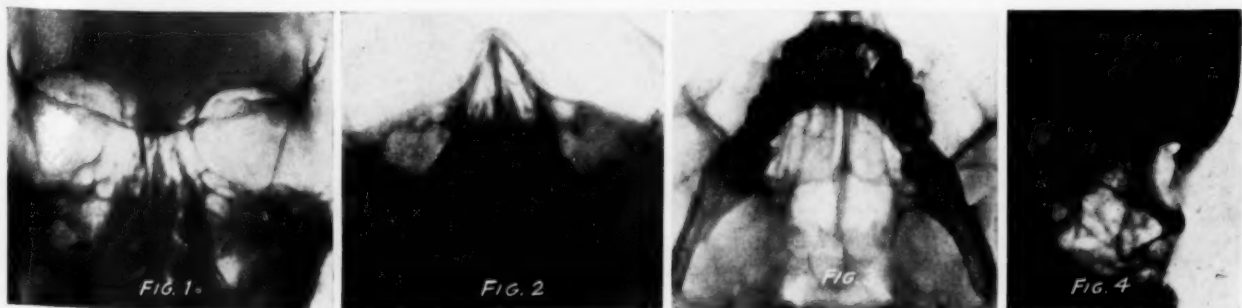
The lateral projection is of prime importance in determining the topography of the several sinuses. It seldom reveals pathological change, owing to

the fact that both right and left sinuses of each of the four groups are projected upon each other. This is one reason why some men do not want a lateral projection. It is, however, a very necessary view, giving, as it does, information not obtainable in any other way. It is of utmost importance that a true lateral view be obtained. This is accomplished by placing the patient so that he lies squarely on his right or left side, the film horizontal and about four and one-half inches above the level of the table top. The head must be in exact normal alignment with the long axis of the spine, and a vertical line must cut the centers of pupils of both eyes. The tip of the nose and the external occipital protuberance must be equidistant from the surface of the film holder. The central axis of the x-ray is directed vertically downward, centered on the external angular process. This view is of utmost value in certain cases in which an absence of frontal cells is to be differentiated from pus filled sinuses. If the frontal bone fails to divide into an anterior and a posterior wall thus forming a cavity in the frontal bone, the indication is that a congenital absence of frontal sinuses exists. If such a separation is seen, then an opaque area between the two walls indicates sinus infection or other pathological condition. The antero-posterior depth of the frontal sinus is determined on this view and this is an index as to the degree of transparency that the frontal sinuses should show on the 23° postero-



Case V.—**Fig. 1**—Frontal-ethmoid: postero-anterior projection, frontals are very large, symmetrical in outline but asymmetrical in configuration, there being almost complete septa in the left which seemingly divide this cell into separate chambers, while there are no such bony divisions in right; both are clear. Ethmoids on left are markedly clouded, while the right side is clear. (Maxillary cells are seemingly clouded.) **Fig. 2**—

Maxillary: postero-anterior projection, both cells are clear. (This definitely rules out the doubtful evidence on 23° projection. **Fig. 3**—Sphenoid: superior-inferior projection, left cell is larger than right, both clear. **Fig. 4**—Lateral projection: very deep frontals (illustration cuts off the sphenoids but original exposure shows these to be large). Posterior ethmoid area definitely clouded.



Case VI.—**Fig. 1**—Frontal-ethmoid: postero-anterior 23° projection, total absence of frontal cells, ethmoids clear on both sides. (Left antrum appears less clear than right). **Fig. 2**—Maxillary: postero-anterior, both antra are clear, ruling out the doubtful evidence of left side pathology seen on Figure 1.

Fig. 3—Sphenoid: superior-inferior projection, both cells medium size, both normal transparency. **Fig. 4**—Lateral projection: shows failure of tables of skull to divide, thus establishing a congenital absence of frontal sinuses, sphenoid area clear (illustration cuts off posterior portions).

anterior plate. On this lateral view one learns of the extent of the horizontal recesses of the frontal sinuses which occasionally are found to extend far posteriorly under the floor of the anterior fossa of the cranial cavity. In some cases this horizontal portion may be the entire extent of the frontal sinus, the vertical portion being absent.

On this lateral view the ethmoid cells are seen to lie posterior to the frontal cavity. The individual cells may be of large or of small size, but are most often of various sizes. Some writers divide these cells into anterior, middle and posterior groups, while other anatomists speak of an anterior and posterior group. Roughly, one can identify these divisions on this projection. Occasionally one is able to see pathological involvement of the anterior group while the posterior group is clear, or vice versa. (Obviously, one cannot distinguish between right and left side involvement on this exposure regardless of which side of the head is placed against the film, but the first projection gives this particular information). Often the foremost of the anterior ethmoid cells will overlap, and sometimes be confused with the frontal cells. They may be seen to also overlap the sphenoid area.

The shadow of the maxillary sinus usually is seen as a large, more or less quadrilateral area of considerable transparency which most often is seen to be quite clear even when there is pathology in one of the antra as seen on the maxillary projections. If both are diseased one usually finds a translucency, although occasionally it has been found to be fairly transparent in spite of the presence of the double infection.

The sphenoid sinus on this lateral projection is seen to lie directly under the sella turcica, and, in the normal condition, is relatively quite transparent to the x-rays. The size of the cells is observed and checked up with that seen on the third, the sphenoid projection. Sometimes these cells are very small or may even be totally absent, as has already been referred to. Variations in extent are often found and there are instances in which they are seen to literally dissect the dorsum sella from below, even entering the posterior clinoid processes. Thus, the normally thin plate of bone is separated into an anterior and posterior wall, a superior recess of the sphenoid sinus lying between them. Some sphenoid cells are seen on this lateral projection to lie entirely in the anterior half of the body of the bone, the shadows of the pos-

terior half being made up of cancellous bone tissue.

In using these four projections the total exposure time must be kept at a minimum by using double screens and a one or two millimeter filter. A satisfactory result is obtained by an exposure of three, four, five and one seconds respectively for the four projections described, using 20 ma. at 5 inch gap. In several hundred cases not a single instance of epilation or other untoward effect has occurred with this technique.

SUMMARY

1. A single exposure of the nasal sinuses is meager evidence on which to base an opinion as to the presence or absence of sinus disease and tends toward errors in interpretation.

2. The two exposure technique, consisting of a frontal and a lateral projection, gives satisfactory evidence as to the frontal and ethmoid sinuses, but the condition of the maxillary and sphenoid cells is not so well determined and therefore should be regarded as an incomplete examination.

3. The four projections, as here set forth, give the maximum information and therefore should be used in the routine examination of the nasal sinuses.

X-Rays and X-Ray Apparatus; An Elementary Course*

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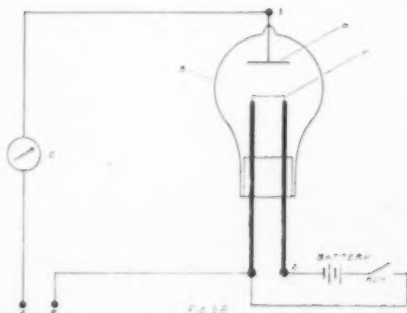
THE COOLIDGE TUBE

THERMIONIC EMISSION OF ELECTRONS

63. It has already been noted that in a Coolidge tube the vacuum is nearly as perfect as modern means of exhaustion can make it. So high is the vacuum that if an attempt is made to use it as a gas tube, no current passes even with 150,000 volts across the tube. How, then, does it operate? To answer that question, it is necessary first of all to explain what is meant by a thermionic emission of electrons. This can best be done with reference to one or two simple experiments. In Figure 58, B represents a highly exhausted glass bulb provided with three electrodes, 3 joined to an inner sheet of metal P; 1 and 2 to the ends of a filament F of fine wire, tungsten for example. Suppose, now, that 1 and 2 are connected to a storage battery by means of which current may flow through the filament

and heat it to incandescence. Suppose, further, that a second circuit is made by joining 110 D. C. terminals (A and B) as illustrated in the figure, where G represents a galvanometer or any sensitive current-measuring instrument. A deflection of G will then indicate a current flowing around the circuit A to G to 3 to plate to filament to 1 to B. Is there any such current? We may distinguish two cases. (1) With filament cold, that is, key open, it is found that, no matter what the polarity of A and B is, no current is indicated by G. (2) With

the filament incandescent (key closed), however, if B is negative, marked current is indicated, whereas if B is positive, no current passes. Evidently, therefore, a current passes through such a tube when the filament is hot and when it is negative. Now, what is the explanation? It is found in the fact that any hot piece of metal is a source of electrons. At the surface of metals a process somewhat akin to evaporation goes on, as a result of which, at high temperatures, there is a copious emission of electrons known as *thermionic emission*. In the above tube, therefore, the hot filament liberates electrons; if the filament is negative, and the plate positive, since negative repels and positive attracts negative electricity, these electrons are driven across the vacuum space. There is, therefore, a current of electricity which, in this case, consists of a stream of negatively charged electrons. If the filament is positive, however, because of the attraction of positive for negative, the electrons cannot escape from the filament and no such current exists.



*Received for publication April 24, 1923.

HOT FILAMENT RECTIFIERS—
THE KENOTRON

64. It should now be evident that if 110 volts alternating is applied to AB, a stream of electrons will cross the tube only during the half cycle when the filament is negative. In other words, an intermittent but uni-directional current flows in the circuit containing G, although an alternating voltage is applied. Such a three-electrode tube, therefore, is an excellent rectifier and has many practical applications. The use of such a valve tube in "Radio" will be familiar to many readers, while we have already made reference (Sec. 38) to such a means of suppressing inverse current. The same principle is utilized in the *Kenotron*, a device perfected by Dr. S. Dushman of the General Electric Research Laboratory, for the rectification of a high tension voltage. How perfect is the rectification, is well shown in Fig. 59, where the upper curve shows the variation in the alternating voltage applied to a kenotron, while the perfect uni-directional, although intermittent, current is clearly shown in the lower curve. For the loan of the original electrotype of this figure, as well as those of Figures 64, 65, 66, 71, 72, 73 my grateful thanks are due Dr. W. D. Coolidge, of the General Electric Company.

65. Now the Coolidge x-ray tube, for which we have to thank the genius of Dr. W. D. Coolidge, is a direct application of the principle of thermionic emission. It differs from the gas tube, not because x-rays originate for any different reason but because the stream of high speed electrons has its origin in an incandescent filament of metal. To heat the filament, an independent circuit, called the *filament circuit*, is necessary. In the original arrangement (Fig. 60), a storage battery B_1 and B_2 was used as the source of supply for this circuit. In the arrangement now on the market (Fig. 61), a branch from the A. C. mains supplies a small filament transformer,

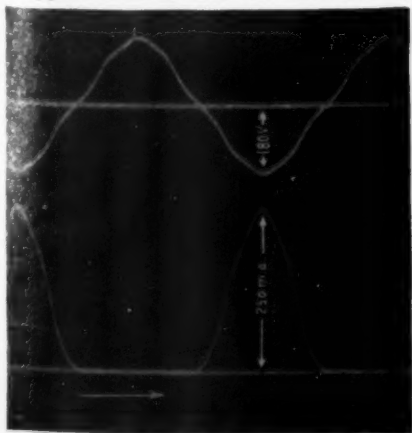


Fig. 59

the secondary of which is connected in series with the filament. While this arrangement is more convenient, it has one disadvantage. Voltage fluctuation on the line will cause corresponding fluctuations in the filament and consequently, as we shall see later, alter the milliamperage through the tube.

To give the necessary high speed to the liberated electrons, the high tension voltage is applied to the tube in the usual way, the hot filament being, of course, negative. Since the whole filament circuit is raised to the high potential of the cathode, it is necessary to insulate the storage battery (or the filament transformer). The complete circuit for the ordinary Coolidge tube, therefore, includes (1) the usual high tension circuit, (2) the filament circuit. In Figure 62 connections for the complete arrangement (minus the synchronous motor circuit) are shown. It will be seen that the high tension circuit, which in this case has the auto-transformer control, is exactly the same as that already discussed. The new feature is the filament circuit controlled by the filament switch and containing an ammeter to enable an operator to read the current heating the filament. By means of a variable inductance (I) the strength of the current may be altered. Before discussing details of control, however, it is desirable next to look at some further points in connection with the tube itself. There are some half dozen types of tube now on the market but in the meantime our remarks shall refer primarily to the standard so-called "Universal" type.

THE UNIVERSAL STANDARD TUBE

66. To obtain the necessary high degree of exhaustion, and to eliminate as much as possible all traces of residual gas, elaborate precautions are taken. "All metal parts before being mounted are fired in a quartz tube vacuum furnace at 900°C . for about an hour, and are allowed to cool down in a vacuum so as to prevent oxidation. The purpose of this firing is to render the parts perfectly clean and to remove partially the occluded gases".¹ During exhaustion the tube itself is heated in an oven at about

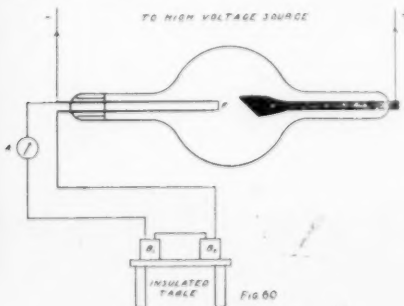


Fig. 60

400°C . for three quarters of an hour. After this process the tube is operated at higher and higher voltages until "all signs of gas have disappeared and the tube is backing up a 10 inch parallel spark gap and the anode is at an intense white heat".¹ Here it may be noted that the presence of harmful amounts of gas is indicated by the appearance of a greenish glow in the bulb. Should a tube which has been in use develop such an appearance, it is an indication of impaired vacuum and re-exhaustion will probably be necessary.

FOCUSING

67. The hot filament, consisting of a piece of fine tungsten wire (0.0085" in diameter) wrapped into a small spiral, is surrounded by a concentric cylinder of molybdenum (C, Fig. 63), the inner end of which projects a little beyond the filament. At the other end of the cylinder, a plane flange of molybdenum is placed. As the cylinder and flange, as well as the filament, are in electrical contact with the high tension terminal, a repulsive action is exerted on the liberated stream of electrons and focusing results. By using filaments of different shapes and adjusting the relative positions of the parts, focal spots of different sizes are obtained. In actual practice, tubes with fine, medium and broad focal spots are constructed.

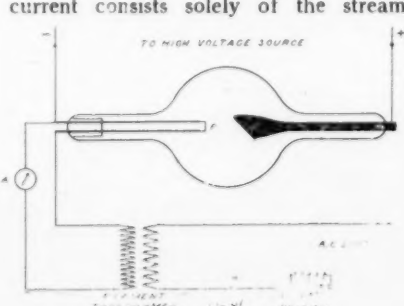
The general principle of the focusing device will be clear from Figure 63. Figure 64 shows a close-up view of the cathode of the radiator type tube (Sec. 73), in which case the flange is replaced by a hemispherical cup.

THE ANODE

68. In the universal tube this consists of a solid rod of wrought tungsten attached to a stem of molybdenum. Figure 65 renders any detailed description unnecessary. As the anode is also the anticathode, the tube has the simple appearance shown Fig. 66.

CONTROL OF TUBE CURRENT

69. In the gas tube we have seen that the residual gas is conducting, the current consisting of a stream of positive ions in one direction, along with cathode rays in the opposite direction. In the Coolidge tube the current consists solely of the stream



of negative electrons liberated from the hot filament. How is the magnitude of this current controlled? In seeking to understand the answer to that question, it is well to recall that an electric current is measured by the total quantity of electricity passing each second any "point" on the circuit. If, therefore, more electrons are transferred every second from the filament to the target, the tube current will be greater. Now work on thermionic emission has shown that the higher the temperature of the hot filament, the greater the supply of electrons. The milliamperage through a tube, therefore, is increased simply by increasing the filament heating current. But it is asked, where does voltage come in? That can be answered with reference to experimental results such as given in Tables VI and VII (taken from Wappler Electric Co. literature). The numbers in Table VI refer to a Coolidge tube, for which the filament current is kept constant at 4.10 amperes.

TABLE VI

Filament Current 4.10 amp.	
Back-up	Ma.
1"	13
1"	15
1 3/4"	18
2 1/2"	20
3 1/2"	21
4 1/4"	21
5 1/4"	21

TABLE VII

Filament Current 4.20 amp.	
Back-up	Ma.
1"	16
1"	18
1"	20
1 3/4"	22
2 3/4"	25
3 1/4"	25
4 1/4"	26
5"	26

By means of the rheostat (or auto-transformer) control, greater and greater voltages are applied to the tube, and for each value, the corresponding tube current measured. It will be noticed that, while at first the tube current increases with increasing voltage, a stage is reached at which increase in voltage produces no increase in milliamperage. Those who prefer to study results in graphs rather

than in tables will see that curve A, Figure 67 shows the same result even more clearly. In Table VII and Curve B, Figure 67, the same result is shown for a different filament current, the only difference in the two cases being that the maximum tube current in the latter is greater. Experiment tells us, then, that *corresponding to each filament current, there is a maximum value of the tube current, which is independent of the applied voltage.* The explanation of this maximum current—called *saturation current*—is simple enough. The available supply of electrons from a hot filament depends on its temperature and therefore on the magnitude of the filament current. Evidently no more

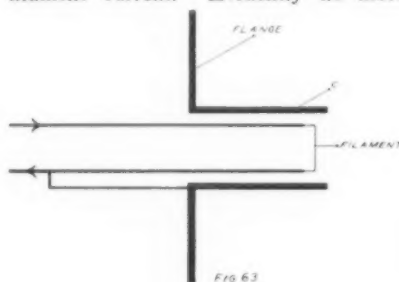


FIG. 63

electrons can be transported across the tube per second than are liberated each second from the filament. At first, when higher and higher voltages are applied to the tube a greater and greater number of electrons is transported each second across the tube. Ultimately, however, a stage is reached at which as many electrons reach the anode per second as are liberated from the filament. Evidently further increase of voltage cannot increase this number (although it will increase their speed), or once more the saturation current has been

reached. In actual practice, the back-up of a tube is invariably great enough to ensure the existence of saturation currents for all filament current values used.

Control of the Coolidge tube current, therefore, depends for all practical purposes, solely on regulation of the filament current whose magnitude is read directly from the filament ammeter. It is, then, highly desirable that the operator of a particular Coolidge tube should know the tube (saturation) current corresponding to each ammeter reading. Such a relation he can readily obtain for himself by taking, for each of several filament current values, a series of tube current values and corresponding back-ups (as in Tables VI and VII) until the saturation stage has been reached. If, then, for each filament current, he records the saturation tube current, he will have a table similar to Table VIII. (a copy of some actual results taken from an early paper by Dr. W. D. Coolidge). By plotting these results, an extremely useful curve similar to that in Figure 68 will be obtained. Figure 69 is a copy of a

TABLE VIII

Filament Current	Tube Current
3.09 amp.	0.6 ma.
3.31 amp.	2.5 ma.
3.40 amp.	4.4 ma.
3.50 amp.	8.2 ma.
3.57 amp.	12.6 ma.
3.67 amp.	20.7 ma.
3.65 amp.	21.8 ma.
3.71 amp.	27.0 ma.
4.13 amp.	35.4 ma.

similar curve for a universal tube taken from recent literature of the Victor Electric Corporation.

In the universal Coolidge tube, therefore, the tube current is controlled by the filament and, if saturation current is used (as is nearly always the case), is independent of the voltage across the tube. (Increasing the back-up does not increase the tube current, but does alter, as we shall see later, the nature of the beam of x-rays leaving the tube). Regulation of milliamperage and of voltage, accordingly, may be made with much greater readiness and exactness than is the case with a gas tube.

THE VOLTAGE STABILIZER

70. In connection with the relation

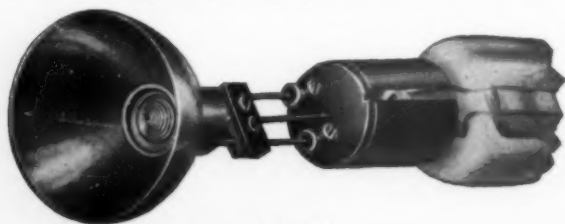


Fig. 64



Fig. 65



Fig. 66

between filament current and milliamperage, it is important to note that a very slight change in the filament current may produce a big change in the tube current. To take some actual numbers from the curve of Fig. 69, with filament current 4 amperes, the tube current is 40 ma., while an increase to $4\frac{1}{4}$ amperes raises the tube current to 100 ma. This has an important practical aspect. Should the filament current fluctuate, there might be marked changes in the tube current; for certain current values "a 10 per cent change in filament current will cause a 300 per cent change in the tube current" (Victor Service suggestions). Obviously this may have disastrous consequences.

Now, if storage batteries are used as the source of supply for the filament circuit, voltage fluctuations are negligible. Unfortunately, however, storage batteries are not so convenient as a filament transformer, and the latter is now almost entirely used. The supply for the transformer is commercial A. C., in which case voltage fluctuations are inevitable. Most read-

ers will have observed a sudden dimming of incandescent lights when, perhaps in another part of the house, an electric iron or toaster is turned on. The voltage applied to the lamps has lowered because of the greater "load" put on. Now, such sudden changes in voltages are almost inevitable when working with a supply used for many purposes and in many places. In using a Coolidge tube, therefore, with filament transformer and no special means for getting rid of voltage fluctuations, marked changes in milliamperage may occur.

By means of a voltage stabilizer, however, it is possible to maintain a constant tube current in spite of voltage fluctuations. The principle of one type of stabilizer² will be clear from a study of Figure 70. In the ordinary tube (high tension) circuit an electromagnet M is placed, near one end of which is a piece of soft iron, the armature A. When a current flows through the tube, M is magnetized and the soft iron piece attracted. Before this piece moves, however, the attraction must be great enough to overcome the tension of a spring S attached to it. Evidently the greater the tension of the spring, the greater the attraction necessary to move the iron, or, in other words, the greater must be the tube current. When A is held away from the magnet (as in figure), the contact point 2 touches the fixed contact point P, so that the filament current flows from transformer to 1 to 2 to P to 3 to 4 through filament and back to the transformer. Should the piece A be pulled towards the magnet, however, contact between 2 and P is broken and the filament current must flow through the resistance R. There are, therefore, two possible filament circuits, one including R which we shall call the high resistance path, the other of low resistance where R is excluded. Corresponding to these two circuits, there will be (for any constant voltage) two possible values for the effective

tive filament current, a maximum and a minimum.

To understand the action of the stabilizer it is necessary to remember that the tube current is intermittent, as is nicely shown in Fig. 71, where A represents the alternating filament current, while B shows the intermittent uni-directional tube current. It follows, therefore, that even with absolutely constant voltage, until the tube current has risen to a certain critical value (which depends on the tension of the spring S), the armature is held away from the magnet. During this interval, the filament current follows the low resistance path. Once, however, the tube current exceeds the critical value, the spring attraction is overcome, the armature moves toward the magnet, the contact points 2 and P are separated, the resistance R is introduced and the filament circuit has the high resistance value. During every half cycle, therefore, the contact points are together part of the time, separated the remainder of the half cycle. In other words, the armature is in a state of vibration, and the resistance of the filament circuit fluctuates between the maximum and the minimum value. Hence the effective filament current has an average value, whose magnitude depends on what fraction of the half cycle R is in or out of the circuit. If the voltage is constant, this fraction remains constant, and the effective filament current is constant.

Now suppose there is a sudden rise in the voltage. This causes a momentary increase in the filament current, a greater emission of electrons, a greater

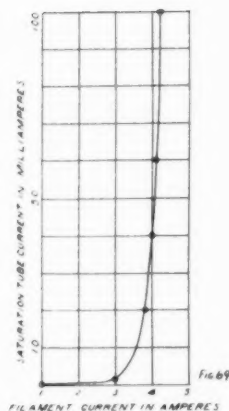


Fig. 69

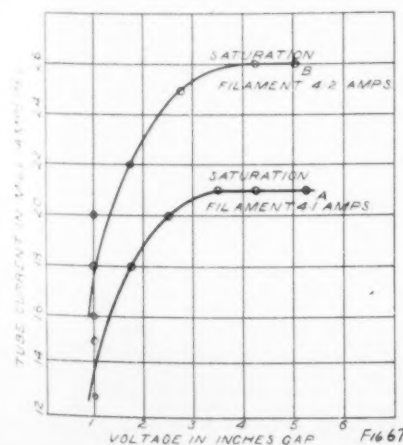


Fig. 68

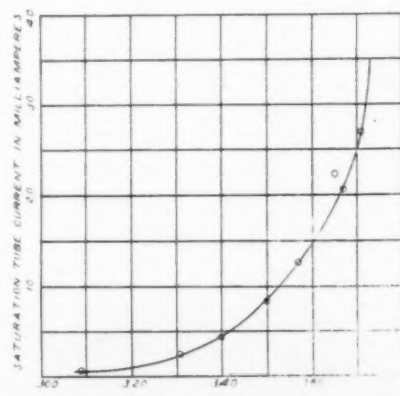


Fig. 68—Filament current in amperes.

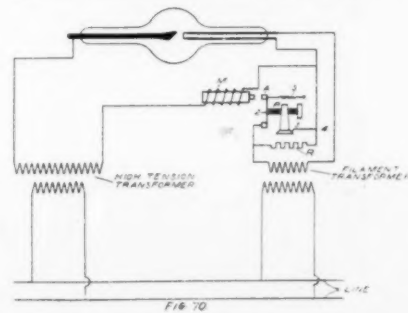


Fig. 70

tube current, a stronger electromagnet, and therefore an increase in the length of time each half cycle the contact points are kept separated due to the attraction of the armature. The filament circuit, therefore, will have the higher resistance path for a greater portion of the half cycle, and the effective filament current will be kept from rising.

On the other hand, suppose the voltage drops. A momentary drop in the filament current is followed by a lower tube current, and a feebler electromagnet, in consequence of which the armature is held away from the magnet for a longer portion of the half cycle. This time the filament circuit has the low resistance path for a longer part of the half cycle, and so the effective filament current does not drop. Thus automatically, for any given setting of the spring S, the filament current is kept constant. The efficiency of the stabilizer will be seen by a glance at Table IX (taken from the article to which reference has been made) and at Figure 71. In curve B it will be seen that the crests of the curve for the same tube current are all exactly at the same level, thus showing the constant value of the current.

TABLE IX

Without Stabilizer		
Time		Tube Current
0	Min.	10.0 ma.
1/2	Min.	9.6 ma.
1	Min.	9.3 ma.
1 1/2	Min.	9.0 ma.
2	Min.	8.7 ma.
2 1/2	Min.	8.1 ma.
3	Min.	7.0 ma.

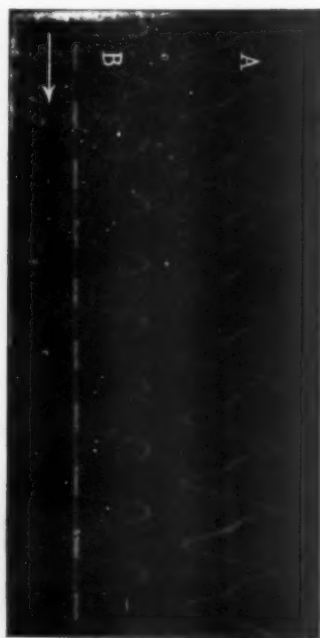


Fig. 71

With Stabilizer		
Time		Tube Current
0	Min.	10 ma.
1/2	Min.	10 ma.
1	Min.	10 ma.
1 1/2	Min.	10 ma.
2	Min.	10 ma.
2 1/2	Min.	10 ma.
3	Min.	10 ma.

IS RECTIFICATION NECESSARY?

71. In Section 64 reference has been made to the rectifying property of a hot filament tube such as the kenotron. It may well be asked, then, cannot the terminals of a high tension transformer be applied directly to the universal Coolidge tube without the necessity of a noisy synchronous motor? As a matter of fact, this can be done *provided the target is kept cool enough*. In practice, however, there is no objection to using the tube with the target extremely hot. Now, once tungsten reaches the temperature of 2000° C. (3300° C. is melting point) it begins to emit electrons. This means that, with the target above this temperature, an inverse stream of electrons is present if no rectifying device is used. Such an inverse current not only gives rise to x-rays from regions in the neighborhood of the cathode (where the inverse electrons hit), but also because of the extreme heat developed at the spot where the electrons hit, increases the danger of a tube puncture. (The danger signal in this case is the appearance of green fluorescence in the neighborhood of the cathode.) With a universal tube, therefore, a rectifying device is necessary; with the radiator tube, however,

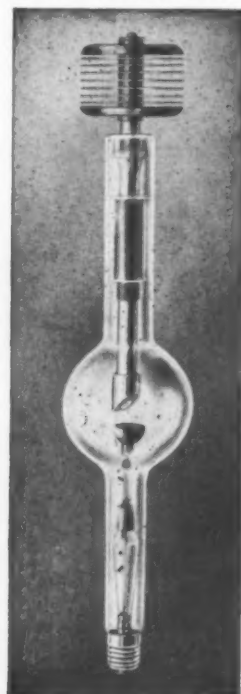


Fig. 72

for reasons given below, this is not the case.

MAXIMUM INPUT

72. The importance of the question of permissible input should be evident from the last paragraph. As in the case of gas tubes, so in the type we are now considering, every tube has a maximum permissible input. The supply of too much energy (volts x milliamperes x time) may melt the target, vaporize the metal, blacken the tube and so increase the danger of tube puncture. Moreover, in the case of a tube used for the long intervals necessary in therapy, the heat radiated from the hot target may cause a rise in temperature of the glass bulb sufficient to liberate gas and possibly to melt the glass. Fortunately, unlike the practice in the case of gas tubes, the maximum input for each type of Coolidge tube is clearly stated. For example, in the case of the 7" universal tube used for radiographic purposes, when operated with a voltage equivalent to a gap of 6" between points, the milliamperage should not exceed 80 ma. for broad focus tubes, 50 ma. for medium focus, 25 ma. for fine focus. Operation on lower voltage would permit, of course, of corresponding higher milliamperage. When this same tube is used for therapeutic purposes, where the time factor may be large, an input of about one kilowatt is permissible. (1 kilowatt = 1000 watts = 10,000 volts with 100 ma., or 20,000 volts with 50 ma., etc.)

THE RADIATOR TUBE

73. In addition to the universal



Fig. 73

tube, other types based on the same general principle, are on the market. There is an 8" bulb for high voltage deep therapy work, constructed along lines similar to the universal tube, together with at least four types of what are called radiator tubes. The four types include (a) the right angle dental, (b) the 30 ma. straight, (c) the 10 ma. straight, (d) the 10 ma. portable. As radiator tubes may be operated directly from the transformer and have proved extremely useful, some details in connection with the 30 ma. type (Fig. 72) will be considered. The essential point to realize is that no rectifier is necessary because the target is never allowed to become hot enough to emit electrons. This is done, (1) by limiting the permissible input; 30 ma. must not be exceeded and that at a voltage not exceeding a 5" back-up (between points); (2) by constructing the anode so that heat is conducted rapidly away from the focal spot.

To prevent the rapid rise in temperature of the anode, its construction differs in two important respects from that of the universal tube. A comparison of Figure 73 with Figure 65 will show the decided difference in the appearance of the two anodes. In the radiator tube, the target consists of a small button of tungsten, attached to a solid head of purified copper, which in its turn is electrically welded to a copper rod. Attached to the outer end of this rod which extends through the anode end of the glass tube, are the copper radiators clearly shown in the illustration. Now, copper is not only a better conductor of heat than tungsten but it has also a higher specific heat (see Table V of previous article). For two reasons, therefore, the temperature of the radiator target rises more slowly, (1) because of its greater heat capacity, (2) because of the greater conductivity of copper as compared with tungsten, combined with the radiating device. Regarding (1) we may note that it takes only 10 calories of heat to cause a rise in temperature of the solid tungsten target (plus stem and iron support), while it takes 81 calories for the same temperature change of the radiator anode. In the radiator tube, therefore, because of the comparatively slow rate at which the temperature rises, combined with rapid cooling, an



FIG. 75

operator, when making radiographs, begins each exposure with a cool target. "With every current source it permits of the intermittent use of more energy than could in practice safely be carried by a tube with a solid tungsten target of the same size of focal spot." (Coolidge). This means, that for the same amount of energy, a smaller focal spot can be used, with consequent advantage which will be seen later. Moreover, because of the mode of radiation, a much smaller sized bulb may be used, the standard size for the 30 ma. type being $3\frac{3}{4}$ ".

On the other hand, the tube for continuous use as in treatment will carry less than one quarter of the energy of the universal tube. But, while it is not designed for heavy work and is recommended by Dr. Coolidge for diagnostic purposes, a 30 ma. tube with suitable transformer is an extremely useful outfit for the private practitioner. The gain which results simply from the absence of the noise of a synchronous motor and rectifying disc is in itself worth much.

74. In conclusion, we summarize some of the important advantages of the Coolidge tube. (1) For all types, the maximum permissible input is clearly stated, (2) the tube current (assuming saturation) is independent of the applied voltage, (3) the tube current can be regulated with the same ease as the strength of the current in any simple electric circuit, (4) by means of a stabilizer remarkably constant tube currents may be maintained for long intervals, (5) there are no vacuum troubles, provided the tube is not abused.

THE LILIENFELD TUBE

75. A brief reference will now be made to a third type of x-ray tube, in which, like the Coolidge, the current consists of a stream of electrons in a highly exhausted tube.³ The tube consists essentially (Fig. 74) of a pointed cathode P placed at a distance of the order of 10 mm. from a small cavity C in the target face of the anode. "The points must be grounded with the greatest care and precision on wires * * * of Wo, Ta, Mo or other refractory metals." Although the cathode is cold, a liberation of electrons takes place from the pointed end, probably because of the electric field which exists between the cathode and anode when a high voltage is applied in the usual way. For the proper operation of this

tube, the vacuum must be even higher than that necessary for a Coolidge tube, and in the initial exhaustion very elaborate precautions must be taken. For these and other details the reader is referred to the original article.

The electrons impinge not on a plane target but on a small cavity in the face of the anode whose size depends on the amount of energy to be supplied the tube. With a plane target, Dr. Lilienfeld states that there "is a tendency to form one or more extremely small focal spots", with consequent danger of melting the target. By means of the cavity, not only is the formation of very fine spots prevented by the resulting alteration in the shape of the electric field, but also use is made of secondary cathode rays generated at the spots where the primary beam strikes. In consequence, the whole cavity acts as a focal spot.

The magnitude of the tube current resulting from a given voltage depends on the sharpness of the pointed cathode, on the distance between anode and cathode, and the general geometric arrangement. Unlike the Coolidge tube, however, (assuming saturation current), the tube current in this case is not independent of the voltage but rapidly increases with it. Moreover, it is claimed, the effective voltage is confined more nearly to the crests of the wave-form than is the case with other types of tube, and for that reason (as shall be seen later) the rays are more homogeneous. But the tube is scarcely yet out of the experimental stage—at least as far as information at the disposal of the writer is concerned—and further details would be out of place in a course of this kind.

FOOTNOTES

- 1—Am. J. Roentgenol. 7:257, June, 1920.
- 2—W. K. Kearsley, Am. J. Roentgenol. 8:864, Oct., 1921.
- 3—J. E. Lilienfeld, Am. J. Roentgenol. 9:172, March, 1922.

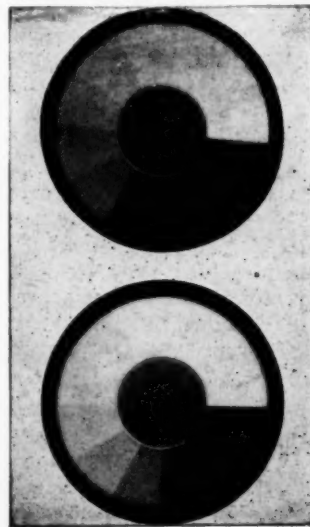


Fig. 76

EDITORIAL

The JOURNAL OF RADIOLOGY

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ANNUAL MEETING

Rochester, Minnesota

December 3, 4, 5, 6 and 7, 1923

The A. M. A. and Radiology

The American Medical Association's formal recognition of radiology as an integral part of medicine completes the laying of the foundation on which American radiology will build in future years.

The following is a copy of a portion of the report of the Reference Committee on Sections and Section Work as adopted at the annual meeting of the American Medical Association held in San Francisco, June, 1923:

"After careful consideration of the report of the Council on Scientific Assembly, we concur in all of the recommendations presented.

1. We especially endorse the recommendation that no changes be made in the number of sections of the Scientific Assembly. This opinion already has had the approval of the House of Delegates as expressed at the St. Louis session.

2. We feel, however, that the Association should recognize the increasing importance of special medical activities, such as radiology, physiotherapy and occupational therapy; and to that end we wish to express our approval of that portion of the resolution offered by Dr. Van Zwaluwenburg which provides that, wherever possible, every section program should contain at least one paper on a subject pertaining to some other specialty of particular interest and importance to members of the section, and your committee makes such recommendation.

3. In view of the fact that laymen are attempting to practice radiology, we recommend that the American Medical Association recognize the science of radiology as an integral part of medicine and surgery."

Respectfully submitted,

Albert E. Bulson, Jr., Indiana, Chairman,
C. E. Mongan, Massachusetts,
L. H. McKinnie, Colorado,
A. W. Booth, New York,
Philip Marvel, New Jersey.

Recognition of radiology as an integral part of medicine by the largest body of medical men in the United

States should be conclusive evidence to the members of the profession that radiology as a science in itself has been thoroughly tried and found worthy.

In view of the fact that similar action was taken some time ago by the American College of Physicians and the American College of Surgeons, every radiologist has a right to feel a new dignity in his work now that the American Medical Association officially bids him enter and present what he may for the advancement of the science as a whole.

Thus a new responsibility is laid upon every radiologist's shoulders, for though he makes no claim to hold the master cure-all for every human ill, he must now sooner or later recognize the fact that his work brings him into almost daily contact with every phase of medical science and that he should have some real information to impart with respect to the advantages and disadvantages of the agents within his control.

A hard rule, surely, but radiology is no place for the physical coward, the mental sluggard, or the moral leper. Its exactions call for unusual fortitude, physical energy, a mind that is never satisfied with past achievements but drives constantly forward to greater things, and more than all else, an indomitable will which holds to the pursuit when pursuit seems utterly useless.

Many of the baffling problems in radiology have been met so that today radiology in some or all of its phases is universally accepted by the profession diagnostically and therapeutically. However, for those who have grown up with the science and have kept their feet on the ground with respect to the proper relation between radiology and medical science as a whole, a tremendous field lies just ahead to be explored and the good thereof applied to the fulfillment of human relief.

That is why the action taken by the American Medical Association provides a source of such great inspiration to the members of the Radiological Society, for it is probably due largely to their efforts that this report was adopted. We take this opportunity to express to the American Medical Association our appreciation.

Clay Emory Giffin, M. D.

On July 22nd Dr. Clay Emory Giffin of Boulder, Colorado, was drowned while attempting to save his thirteen year old son, Elbert, from a like fate.

The family and a few friends had gone for a picnic supper on the banks of Boulder Creek above Eldora. The boy had gone in wading while the doctor stood nearby watching him. Suddenly the lad stepped into a beaver hole and the undercurrent swept him down. Dr. Giffin plunged in to save his son but the undercurrent caught him also and in spite of the truly heroic efforts of his companions he was drowned and for more than an hour it was impossible to recover his body, and then only by dragging the stream with barbed wire. The son, however, was saved.

Dr. Giffin was born in Boulder, March 31, 1882, the son of Dr. and Mrs. L. M. Giffin. He was educated at Mapleton grade school, Boulder Preparatory School and the University of Colorado where he was a member of the Delta Tau Delta, popular among his fellow students and a leader in his class work. He received the degree of A. B. from the University of Colorado in 1905 and

in 1907 was granted the degree of M. D. by the University of Colorado School of Medicine, in which his father held the position of dean for a number of years.

In 1909 he was married to Miss Vera Greenman of Boulder. The two had been classmates throughout most of their school days. Two children, Elbert and Clay, Jr., were born to them. He is survived also by a brother, Horace, a half-brother, Luman, a sister, Mrs. Emory Lines and a half-sister, Grace.

Dr. Giffin entered the practice of medicine with his father and this association continued until the father's death in January of this year. The doctor was intensely interested in his profession and rapidly rose to prominence. He had been a lecturer at the University School of Medicine for a number of years and had recently been appointed Chief of Staff of the Boulder County Hospital. He was a member of the American Medical Association and of the Radiological Society of North America. During the years 1919 and 1920 he acted as the Radiological Society's counselor for the states of Colorado and Wyoming, and he also served as a member of the editorial staff of the official organ of the Radiological Society, the *Journal of Radiology*, up to the time of his death.

He was a scholar, a man of high professional and personal ideals and beloved by all who came in contact with him. In the death of Dr. Giffin the community has lost one of its most prominent and loved citizens and the Radiological Society of North America has lost one of its most loyal members.

Annual Meeting American Roentgen Society

Among the forthcoming important meetings of special societies is the annual convention of the American Roentgen Ray Society. This is to be held in Chicago from September 18th to 21st, with headquarters at the Congress Hotel. A number of eminent foreign contributors will appear on the program, and the announcements indicate that treatment by high voltage x-ray will have a prominent place on the program. Among the papers to be read are the following:

- "Some Aspects of the Cancer Problem"—Robert Knox, M. D., London.
- Title to be announced—Prof. Walter Friedrich, Germany.
- "Radium and Roentgen Rays as Different Agents in Superficial and Deep Therapy"—Albert Bachem, Ph. D., Chicago.
- Title to be announced—Henry J. Ullman, M. D., Santa Barbara, Cal.
- "A Review of Therapy as Seen on the Continent"—I. Gerber, M. D., Providence, R. I.
- "The Effect of Roentgen Rays on Bone Marrow"—Ernest Falconer, M. D., Laird H. Morris, M. D., Howard E. Ruggles, M. D., San Francisco.
- "Technique of High Voltage X-Ray (Combined with Radium)"—Charles Goosman, Cincinnati.
- "Therapy of Abdominal Tuberculosis and Tuberculosis of the Foot (Bone)"—Geo. H. Steele, M. D., Oshkosh.
- "Cancer Therapy from the Surgeon's Standpoint"—Emil Beck, M. D., Chicago.
- "Measurements of Four Different Types of High Voltage X-Ray Machines by the Duane Method and the Friedrich Iontoquantimeter"—George E. Pfahler, M. D., Philadelphia.
- "Roentgen Cachexia"—Charles L. Martin, M. D., Dallas.
- "X-Ray Treatment of Fibroids of the Uterus and Uterine Bleeding Not Due to Malignancy"—John G. Williams, M. D., Brooklyn.
- "Effects of the Shorter Wave Therapy on Gastric Secretion of Dogs"—Sidney Portis, M. D., and Robert Arens, M. D., Chicago.

- "The Platinocyanide Pastille in Deep X-Ray Therapy"—A. H. Pirie, M. D., Montreal.
- "High Voltage Treatment in a Series of Sarcoma Cases"—W. S. Lawrence, Memphis, Tenn.
- "The Control of Hyperthyroidism"—Kennon Dunham, M. D., Cincinnati.
- "Evolution of X-Ray Therapy"—Albert Soiland, M. D., Los Angeles.
- "Hepatic Changes in a Case of Lymphosarcoma Treated by Deep Irradiation"—James T. Case, M. D., Battle Creek, Mich., and A. S. Warthin, M. D., Ann Arbor, Mich.
- "Technique and Statistics in the Treatment of Superficial and Accessible Malignancy with Radium, Roentgen Rays and Electrothermic Coagulation"—J. Thompson Stevens, M. D., Montclair, N. J.
- "Dosage Methods, a Comparison and Deduction"—Otto Glasser, M. D., Cleveland.
- Title to be announced—Charles A. Waters, M. D., Baltimore.
- "The Problem of Deep Therapy"—Gustav Bucky, M. D., Germany.
- "The Value of X-Ray in the Diagnosis of Atypical Pregnancies with Report of Two Cases of Anencephaly Before Birth"—Davis Spangler, M. D., Dallas.
- "Organic Hour Glass Contracture of the Stomach with Some Reference to the Surgical Treatment"—Howard P. Daub, M. D., Detroit.
- "Multiple Osteomyelitis"—Preston M. Hickey, M. D., Detroit.
- "Bone Dystrophies of Small Pox"—John W. Cathcart, M. D., El Paso, Texas.
- "Hydronephrosis"—Bernard M. Nichols, M. D., Cleveland.
- Title to be announced—A. B. Moore, M. D., Rochester, Minn.
- "A New Water Cooled Tube"—C. N. Moore, M. D., Schenectady, N. Y. (General Electric Co.)
- "X-Ray Evidence of Colonic Secondary Reactions"—R. Walter Mills, M. D., St. Louis.
- Title to be announced—Arial W. George, M. D., Boston.
- "An X-Ray Study of 1500 Children Before and After Tonsillectomy Under Ether"—J. H. Green, M. D., Rochester, N. Y.
- "Back Injuries"—William B. Bowman, M. D., Los Angeles.
- "The Upper Left Quadrant"—E. C. Koenig, M. D., Buffalo.
- "X-Ray Study of the Thymus Gland"—George W. Grier, M. D., Pittsburgh.
- "Lateral Roentgenography in Pulmonary Abscess"—L. T. LeWald, M. D., New York City.
- "Carcinoma of the Gastro-Intestinal Tract Accompanied by Bone Metastases"—E. L. Jenkinson, M. D., Chicago.
- "Differences in Destruction of Cartilage in Tuberculosis and Pyogenic Arthritis"—P. B. Phemister, M. D., Chicago.
- "Tuberculous Lobar Pneumonia"—L. R. Sante, M. D., St. Louis.
- "Observations Upon Opaque Residues in the Colon: Report of One Case Harboring an Opaque Meal in the Colon for Five Weeks"—E. H. Skinner, M. D., Kansas City, Mo.
- "Dental Pathology as Revealed by the X-Ray Examination and Underlying Principle of Treatment"—A. F. Tyler, M. D., Omaha.
- "Some of the Pitfalls in the Roentgenographic Diagnosis of Colonic Lesions with Suggestions as to the Proper Method of Overcoming the Same"—Wm. H. Stewart, New York City.

- "Healed Miliary Tuberculosis of the Lungs"—E. B. Blaine, M. D., Chicago.
- "Is Haudek's Niche as Diagnostic of Ulcer as Believed?" Anthony Bassler, M. D., New York City.
- "Chondrogenesis Imperfecta (Achondroplasia)"—Philip Lewis, M. D., and E. L. Jenkinson, M. D., Chicago.
- "Reasons of Lack of Positive X-Ray Findings in Many Cases of Low Back Pain"—Paul B. Magnuson, M. D., Chicago.
- "Teleoroentgenography as An Aid in Orthopedic Measurements"—Preston M. Hickey, M. D., Detroit.
- Title to be announced—Lewis G. Cole, M. D., New York City.
- "The Future Relations Between the Medical and Dental Professions"—Byron C. Darling, M. D., New York City.
- "Extraction of Foreign Bodies from the Organism in Daylight with X-Rays"—Carlos Heuser, M. D., Buenos Aires.

The X-Ray in Africa

"Accept our thanks for your gift of \$1,000 for equipment. We are planning with this to put in the much needed x-ray apparatus. We have so many fractures here, due to the environment these people are living in. They are brought to the hospital and we set the bones by the eyesight in the tips of our fingers, but what a joy it would be to actually see the whole mischief by the x-ray. This is a cocoanut country and thousands of cocoanut trees grow up and down this coast. The trunks of the trees are without limbs, from twenty to sixty feet high, and the boys must climb these trees, which are like greased poles, to gather the fruit. This must be done very often, and when they fall from one of these trees they are quite badly smashed up. The other day I was called up country to see a boy who had fallen from a tree; his arms and several ribs were broken, and this happened four days before I was called.

"Or again, an example like Tinga. One morning he was led in by a boy; his clothes had been torn off from him and he was bleeding from his face, his eyes were tightly swollen shut and his arms and hands were swollen to twice their normal size. His story was that he had just returned from Johannesburg and had fallen among thieves. They tied him down with wires and tried to gouge out his

eyes, also pounded him with clubs in the endeavor to make him tell where he had his money. Tinga, today, with one eye and one arm paralyzed (due to the fact that we did not have an x-ray to see the real mischief) can be found at an outstation doing his bit.

"The above illustrations will show you how much we need this apparatus."

C. J. STARFFACHER, Inhambane, Africa.

*Missionary News, July, 1923.

Technician's Certificates

It has been my good fortune to see the certificates which are being issued to technicians who have successfully passed the examination given by the Registry of Radiological Technicians. The certificates are engraved on pure white vellum paper 8 by 11 inches in size and are signed by the officers of the registry. It will be recalled that this board was fostered by the Radiological Society of North America but that the American Roentgen Ray Society, the Canadian Radiological Society and The American College of Surgeons are cooperating.

The certificate must be renewed annually and is of value only when the holder is employed by a properly licensed medical or dental radiologist. The certificate is proof that the holder has attained a high grade of proficiency in the technical work connected with the practice of radiology.

American Roentgen Ray Society

THE ANNUAL MEETING of this organization will take place in Chicago, September 18th to 21st, inclusive, and it is prophesied that this will be a banner year in its history. The meeting is to be held in the Congress Hotel, on the lake front.

Dr. Hollis Potter, president-elect, and chairman of the program committee, has planned that the program shall have fewer papers and more detailed discussion than has been the plan heretofore.

Central Illinois Radiological Society

THE Central Illinois Radiological Society at a recent meeting elected the following officers:

President James H. Finch, M.D., Champaign
Vice-President Harold Swanberg, M.D., Quincy
Secretary-Treasurer P. B. Goodwin, M.D., Peoria

NEW EQUIPMENT

Acme-International Precision Type Micro-Timer

THE Acme-International X-Ray Company has recently completed the development of their Precision Type Micro-Timer, which now is offered to the profession as an instrument especially accurate on extremely short exposures.

This apparatus is a serial timer of more than normal accuracy. The Timer has two ranges; the upper from 0 to 3 seconds in steps of $1/20$ seconds and the lower from 0 to 30 seconds in steps of $1/2$ seconds. The change from high to low is made by means of a simple switch on one side of the case.

Setting of the Timer for the exposure required is made by a handle with an indicator which actuates a ratchet mechanism. This enables the operator to make the setting either on the dial or by counting the clicks, the latter being the method preferred in some laboratories. The Timer is driven by a constantly operating motor started by a switch opposite the scale changer on the case. Fluctuations in voltage do not affect the speed of this motor, and, therefore, do not affect the accuracy of the Timer.

The timing element is put into operation by an electro-magnetic relay which operates instantaneously, and, as the parts of the timing element are extremely light and the motor speed is unaffected by load there is no loss of time due to inertia. The above points, coupled with the simple construction of this instrument, assure extreme accuracy on very short exposure and prevent its getting out of adjustment.

When the indicator is set at the required time on the dial the timing element is put into operation by pressure on either a push button at the end of the cord or by a foot switch on the floor. The exposure is automatically terminated at the end of the period for which set by an oil immersed circuit breaker built as a separate unit but included in the timer circuit. Release of the push button automatically resets the timer and as many exposures as desired of the same time can be made without resetting the indicator.

In case of emergency the exposure can be terminated at any time simply by releasing the pressure on the push button or foot switch. When fluoroscopic work is to be done the indicator is set at a point on the dial marked

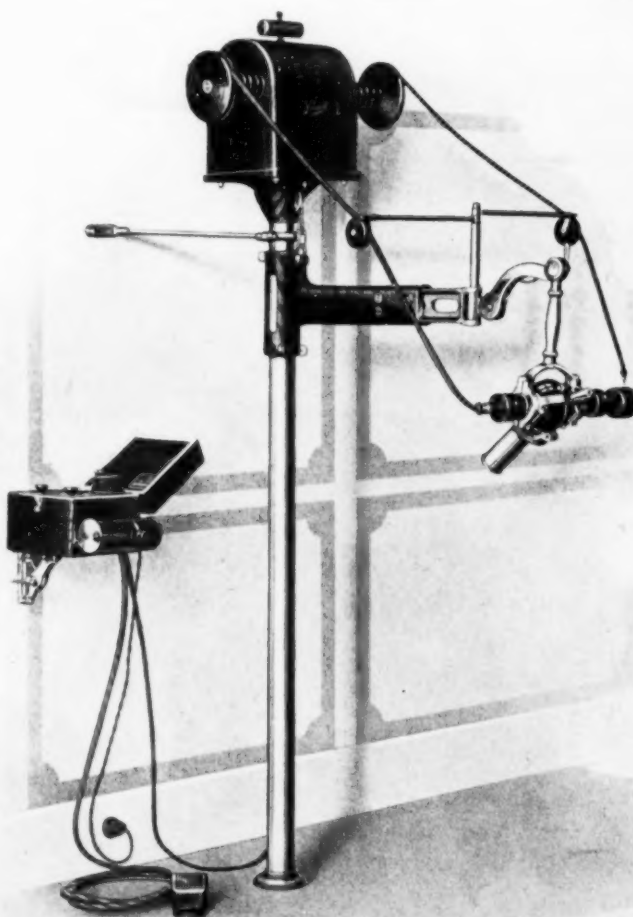
"Fluoroscopic." The circuit breaker when the exposure is automatically terminated. This instrument is finished in black enamel, polished aluminum and nickel plate.



Campbell Dental X-Ray Machine

Briefly, the principle features of this outfit are that the transformer and high tension wires are high up and well out of the way, that the trans-

former has a capacity of 30 milliamps with a 3", 4", and 5" back-up which can be varied as desired, thus fitting the machine to do any class of



work and not limiting the operator to merely dental work as is the case with the 10 ma. 3" back-up machine. The tube stand is specially well designed for convenience in getting any desired position for both dental and general

radiographic work. The outfit takes up a very small amount of floor space, uses the 30 ma. Coolidge tube, and the currents are all very easily operated from the control box mounted on the wall as shown in the picture, ex-

posures being made by the foot switch. The price of this outfit, complete, as pictured including a 30 ma. Coolidge tube and lead glass tube shield is \$875.00.

Portable Ionization Chamber for Deep Therapy X-Ray Measurements

DR. A. MUTSCHELLER, of the Research Laboratories of the Wappler Electric Company, has designed a special new instrument, the Portable Ionization Chamber, for standardizing and measuring the characteristics of deep therapy x-ray machines. Accurate measurements have been impossible with the measuring instruments heretofore available, such, for example, as the iontoquantimeter, the selenium cell, or the large beam ionization measuring chamber.

The most important factors for which deep therapy x-ray machines should be tested are:

1. The correct filter thickness for the machine under consideration.
2. The effective wave length of the x-radiation.
3. The percentage of useful x-radiation which passes through the proper filters when used with that machine.

Dr. Mutscheller has worked out a method by means of which these three important factors may be determined with the Portable Chamber and publication of this method will shortly be made.

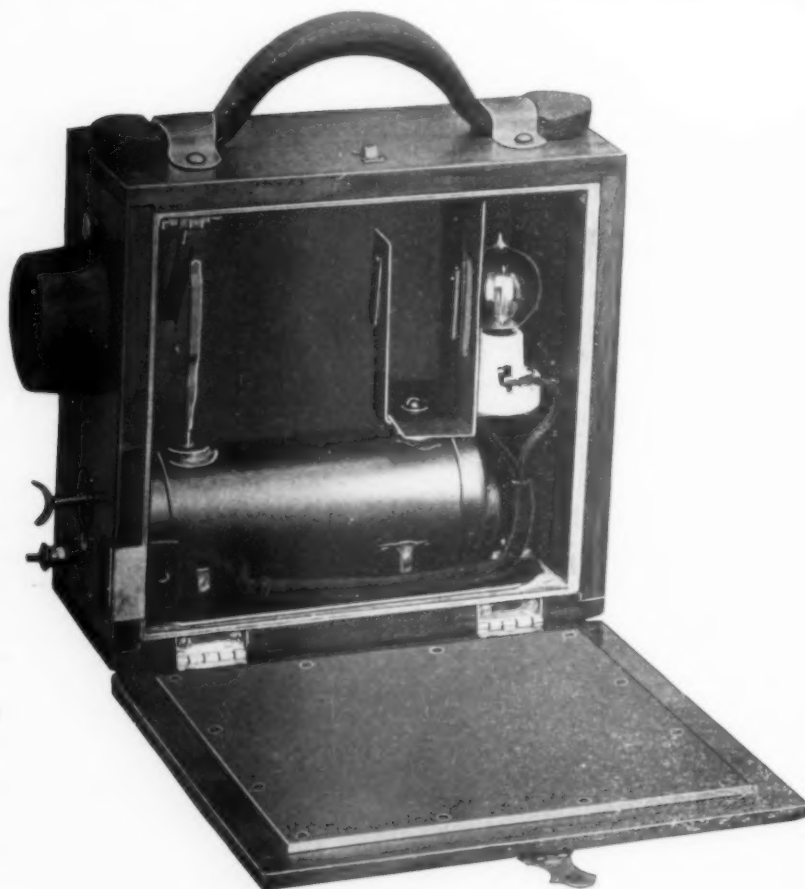
The Portable Ionization Chamber has, first, a carefully constructed metal

ionization drum. Mounted directly upon it is a thin metal leaf so illuminated that its shadow is projected upon a scale readable from the exterior of the lead lined box in which is mounted the ionization drum, leaf, etc. The leaf is so protected that when not in use the entire apparatus can be carried about without risk of damage. It is interesting to note here that a thin metal leaf superior to gold leaf has been found for the proper application of Dr. Mutscheller's method of testing x-ray apparatus with the Portable Ionization Chamber. This metal leaf, it has been found, indicates a much more nearly correct measurement than does any other indicating device. The charging mechanism is very simple and positive.

Dr. Mutscheller's object in designing the Portable Ionization Chamber was to put at the disposal of every radiologist an instrument which would enable him to test the radiation produced by his own x-ray apparatus, to accurately record the dosage, and to exactly duplicate the radiation used by any other radiologist as recorded by means of the Portable Ionization Chamber.

It has been charged that no two radiologists use the same x-ray radiation, nor are capable of reproducing the same x-ray radiation used by another. This may account for the many failures reported in x-ray therapy. Failure for any such reason could have been avoided if the proper measuring instrument had been available.

It is our belief that in the Portable Ionization Chamber, as briefly described, the proper instrument is available, and that in the future it will be entirely possible for the radiologist to accurately record the dosage used so that an exactly similar dosage can be reproduced at any time and at any place.



ABSTRACTS *and* REVIEWS

First Aid X-Ray Atlas of Fractures and Dislocations. First Aid X-Ray Atlas of the Arteries. By H. C. Orrin, O. B. E., F. R. S. C., (Edinburgh). Surgeon, Ministry of Pensions Orthopedic Hospital; Late Civil Surgeon to the London General Hospital; Examiner in First Aid to the Injured; Etc., Etc. Price, \$1.00 each. 1923. Paul B. Hoeber, New York.

THESE are two little 16 mo books, the one on fractures comprising 76 pages and 46 figures, the one on the arteries comprising 46 pages and 11 figures. They are very legibly printed on paper of good quality and bound in stiff board covers.

They are what the names imply—first aid atlases presenting x-ray anatomical studies of the chief bones and arteries of the human body.

Normal and fractured bones are pictured side by side. Causes, signs and treatment are described in the text and illustrations of bandaged fractures are given.

In the second book named, the main arteries and their branches are pictured in roentgenograms, their relationship to the osseous system is precisely shown, the course of each is described and the pressure point for control of hemorrhage is pointed out. One chapter is devoted to an anatomical description of the heart.

The books are adequately indexed and are very useful little volumes for the purpose in view.

Digestive Disturbances in Infants and Children. Roentgenologically Considered. By Charles Gilmore Kerley, M. D., Consulting Physician to the Babies' Hospital, New York; Leon Theodore LeWald, M. D., Professor of Roentgenology, New York University, Roentgenologist to St. Luke's Hospital, New York. With a Note on the Surgery of Infants by William A. Downes, M. D., Clinical Professor of Surgery, Columbia University, Attending Surgeon Babies' Hospital and St. Luke's Hospital, New York. Quarto, Extra Cloth. Price \$12.00. New York, Paul B. Hoeber, 1923.

THIS is the third volume of the *Annals of Roentgenology* (Vol. I, *Mastoids* by Law; Vol. II, *The Pathological Gall-Bladder* by George and Leonard), edited by James T. Case,

M. D. The binding as in the preceding volumes is very handsomely done in extra cloth, paper of extra heavy stock printed in large type. The illustrations are well done.

In his preface the editor remarks that only the rare roentgenologist can hope to specialize in more than one or two branches of his art and must therefore often seek aid outside of his own experience and early training in roentgenology. To such men this book supplies a diagnostic guide in dealing with gastro-intestinal disturbances in infants and children.

The authors in their extensive experience with this phase of gastro-intestinal work have found that the usual diagnostic methods fail to lead the way to proper therapeutic measures. They found also that many cases of chronic gastro-intestinal disease have their origin in childhood and that roentgen diagnosis at this period of life often points the way to early elimination of such disease conditions, thus insuring freedom from otherwise inevitable gastro-intestinal trouble in adult life.

The actual text with its 80 pages interspersed with 49 illustrations describes the technique of the roentgen examination in so far as it differs from the technique used in adult cases. Specific description, so far as the roentgenological diagnosis makes it necessary, is given of the various diseases which the atlas illustrates.

The headings of this textual portion of the book are as follows: Preface—A Note on the Surgery of Infants; Chap. I—Technique; Chap. II—Esophagus (atresia, stenosis, cardiospasm); Chap. III—Stomach (congenital hypertrophic pyloric stenosis, pylorospasm, chronic dilatation, ptosis, syphilis); Chap. IV—Intestinal Tract (dilatation and ptosis of cecum, appendicitis, congenital dilatation of colon, Hirschsprung's disease, intussusception, volvulus, non-rotation of colon); Chap. V—Influence of Posture on Digestion; Chap. VI—Hernia of the Diaphragm; Chap. VII—Tuberculous Peritonitis; Chap. VIII—Transposition of Viscera; Chap. IX—Abdominal Tumors; Chap. X—Foreign Bodies in the Alimentary Tract.

The atlas portion follows this section and is arranged, in general, upon an anatomical basis with a practical use of letters and arrows. It consists of 54 plates totaling 117 figures accompanied

by captions totaling about 50 pages of print in English, French and Spanish. These captions give the clinical history (in some instances completely followed up), the roentgen findings, treatment instituted and a paragraph of comment upon the whole case. The roentgenologic diagnosis of each case has been proved either by prolonged clinical observation or by operation.

The Twenty-Fifth Anniversary Dinner. Editorial, J. Roentgen Society, 19:99-108, July, 1923.

THE oldest radiological society in the world, the Roentgen Society of Great Britain, celebrated its twenty-fifth anniversary in March of this year with many distinguished visitors and members present.

A most enthusiastic meeting, filled with a spirit of hope and good will, is reported in the July journal of that society and anyone who gives too great credence to the legend of the Englishman's lack of a sense of humor should read the above account to enjoy the sparkle manifested at the dinner given in celebration of that anniversary.

Sir Humphrey Rolleston, the President of the Roentgen Society, in his toast to the Society, laid much stress upon the fact that from the very beginning the Society had combined in its membership medical men, physicists and instrument makers and had stood for "team-work" long before that phrase became a catch-word.

Prof. F. A. Soddy, past-president of the Society and winner of a Nobel prize, responded to this toast. The combination always existent in the Society and working harmoniously together argued well, he thought, for that future time when the world, tired of the present mess it is in, should decide upon getting back to a sane mode of living. Doctors and engineers play a mighty part in sociology and there is going to be still greater opportunity for them to exercise their powers and influence upon social progress as time goes on and the world settles down. Prof. A. W. Porter in his response recalled the early days of x-rays and commended the work done by the Society.

Dr. Robert Knox proposed the toast to the visitors and after a tribute to the physicists present gave a brief summary of Dr. Forssell's work in the field of Swedish radiology, referring

to Stockholm as a world center of radiology with Dr. Forssell at its head. Dr. Forssell responded by saying that no society in the world had a better right to look backward with satisfaction and forward with hopefulness than had the Roentgen Society and as proof recounted the names of Thomson, Rutherford, Barkla, the two Braggs, Aston, Soddy, Mackenzie Davidson, Lewis Jones, Deane Butcher, C. R. C. Lyster, Ironside Bruce, Holland, Knox, Barclay, Russ and Kaye, and others. The bridge to the promised land in radiology, he said, leads by way of special institutions for research and teaching and Great Britain is on the right track. Prof. W. Eccles (Vice-President of the Institution of Electrical Engineers) also responded recalling inspiring memories of Prof. Silvanus Thompson. He told of how a student of Thompson's went out to South Africa in the days of the Rhodesian gold rush, and, "being of too trustful a temperament, joined a small party in a trek for gold. One morning he awoke to find himself deserted and robbed, and he could do nothing but tramp to the coast, living on such small animals as he could kill and eat and avoiding such large animals as would have killed and eaten him. When he arrived back in civilization he was indeed a curious figure, with his long hair and virtual nakedness, but he had a large book under his arm, *Dynamo-electric Machinery*, by Silvanus Thompson.

Dr. F. W. Aston, noted physicist and winner of a Nobel prize, toasted the past-presidents of the Society in a very witty speech to which Dr. C. W. Mansell-Moullin and Mr. A. A. Campbell-Swinton responded. The former referred to the fact that "when the Society was young and small it was snubbed by the bigwigs of the medical profession, and boycotted by the medical journals, and for this reason it succeeded." Dr. Swinton referred to Dr. Aston as a "prince of experimenters", citing especially his work on the isotopes of the elements.

Dr. C. Thurston Holland proposed the health of the President, Sir Humphrey Rolleston, saying that his presence in the chair would add to the prestige of radiology throughout the world and paying tribute to him as a great leader, a writer and a man.

Dr. Holland said that of two speeches he might make he had chosen the longer one in response. The shorter one was "I thank you", the longer one "I thank you very much"—and if the bigwigs of the medical profession had once snubbed the Society, the Society was not retaliating

in like kind, proof of which was that they had asked him to accept the presidency

X-Rays and Diagnosis. C. Thurston Holland, M. D. (Sixth Silvanus Thompson Memorial Lecture), J. Roentgen Society, 19:123-148, July, 1923.

DR. C. Thurston Holland, "the father of radiology in England", discussed his subject under four divisions, namely, the bones, the thorax, the gastro-intestinal tract, and stones in the genito-urinary tract.

The universal application of radiography to bone injuries and disease is not altogether an unmixed blessing, he believes, because the present day medical student does not cultivate the same accuracy of observation which used to be necessary and which at times still is necessary in dealing with bone lesions. The usefulness of x-rays in the field of bone lesions has never been questioned from their first advent.

The first kidney stone shown by x-rays and later removed at operation was done by McIntyre of Glasgow in 1896. Leonard of Philadelphia did the pioneer work in establishing the x-ray diagnosis of stone and today "radiology is the only method of examination which can be relied upon to demonstrate the presence of stone in kidneys or ureters. * * * Exploratory operation for kidney stone is a thing of the past."

Stones may be multiple, may exist in only one side or in both or may be in one kidney and the opposite ureter. Symptoms may appear on one side and the stone be in the opposite side. Pure uric acid stones cannot be shown by the x-ray; it is well to remember this in cases which yield no findings under the rays.

Gross intrathoracic lesions may not be diagnosable by ordinary means but the lesion may be unmistakably revealed by x-rays. "Radiography has set a very distinct limit on the value of both auscultation and percussion, and it has proved beyond any possibility of argument, that, valuable as they are, they cannot be relied upon to reveal the whole truth and nothing but the truth." Early aneurysm of the thoracic aorta is mentioned as reliable as positive diagnosis in this connection. Negative diagnosis is almost as reliable as positive diagnosis.

In pulmonary tuberculosis clinical diagnosis is often a matter of conjecture and often when physical signs are lacking the x-rays will show extensive involvement. In a case of recognized pulmonary tuberculosis the x-rays will reveal more than the most skilled clinician can possibly detect unaided. The

plates may not always differentiate between an old quiescent case and one which is active but taken in conjunction with other signs they will in most cases clear up whatever doubt there is. In suspected root infection they alone can decide. In the employment of artificial pneumothorax the use of the rays is of such importance that "to neglect to use radiographic control is criminal". It is not sound medicine to expect the x-ray findings to stand alone in the diagnosis of pulmonary tuberculosis. They must be considered together with the other facts and can not otherwise demonstrate their true value.

In his conclusion regarding this subject the author says that "no case of phthisis should be treated without x-ray examination and without x-ray control. * * * if the most important single method of examination is a duel between the stethoscope and the x-ray in competent hands the x-ray wins easily. Give me the history, let me see the patient, let me make an x-ray examination; you can have the same advantages but a stethoscope instead of x-rays. I know who will have the best of it." Every hospital or sanatorium for consumptive patients should be fully equipped to do this x-ray work with a skilled radiologist in charge of the department.

English dentists have been very slow to recognize the x-ray but modern dentistry is impossible without this aid. "Except from the point of view of a simple stopping no tooth should be treated without an x-ray examination both before and after treatment. Crowning teeth without a previous x-ray examination is absolutely malpractice; the clearing out of root canals and the putting in of root fillings comes under the same category. Bridge work is anathema. A very short experience of undiscovered mysteries of dental conditions as seen by the radiologist would quickly lead to the above dogmatism." If these conditions were adhered to there would be less arthritis or osteo-arthritis.

Esophageal diagnosis is another triumph of radiology.

Sir Berkeley Moynihan is quoted to illustrate Dr. Holland's own views upon gastric diagnosis. The quotation reads: "In the diagnosis of gastric ulcer it (x-ray diagnosis) has pride of place, in competent hands it is far more accurate than any other method of diagnosis, clinical or chemical, or than all other methods combined. It is, indeed, so trustworthy that unless a diagnosis of gastric ulcer made upon clinical evidence is confirmed by the radiologist it should rarely, if ever, be accepted." With delightful humor

Dr. Holland goes on to contrast present day insistence upon roentgen examination of the gastro-intestinal tract with the attitude met with in earlier days when learned anatomists looked askance upon the radiologist attempting diagnosis in this field.

Regarding the hour-glass stomach he says the common typical constriction with ulcer or ulcers is rarely malignant, especially in women, and should be operated upon. However, the atypical hour-glass without a definite cavity and with ragged edges at the site of the constriction is a subject of suspicion, especially in males.

Chronic atony of the stomach without accompanying organic disease does not exist.

In duodenal ulcer the chief function of x-ray diagnosis is confirmatory.

Prejudice, jealousy, honest disbelief, all have stood in the way of x-ray diagnosis but, as is always the way with truth, it has come into its own. One great stumbling block has been and still is that all x-ray work is not of the same standard of excellence. The technique, plates, and interpretation of some workers are not to be relied upon and yet are relied upon, sometimes in high places. "The younger generation of our profession has grown up with a knowledge of x-ray diagnosis which their predecessors did not have and the future of radiology is full of promise. In conclusion, then, is one word of warning which I would say. At present in our teaching hospitals a little too much is being asked from radiologists; it is often the case that they are expected to make diagnosis from the x-ray alone. This is not fair and it is not calculated to advance either the art of radiology or that of medicine. The x-ray is one method used for arriving at a correct diagnosis, and although it is both dramatic and final in many cases, in others it is to a large extent influenced in its reading by a knowledge of other facts. The other part of my warning is that students are being taught too much to rely upon the x-ray departments for their diagnosis and are neglecting to develop to its full the art of observation and deduction so wisely used by our ancestors."

The Journal of the Roentgen Society in its July number has paid a tribute to the Journal of Radiology by quoting verbatim the account which appeared in the editorial section of our May number relating the Sultan of Sulu's one-time adventure in the x-ray field.

Wilhelm Conrad Roentgen. Goesta Forssell, M. D., *Acta Radiologica*,

2:101-109, No. 6, May, 1923.

DR. Goesta Forssell in this article has given an interesting and human sketch of the late Wilhelm Conrad Roentgen and bestows upon him rare praise not alone as a scientist but as a man.

An excerpt from a recent letter of Roentgen written to E. L. Albert, a friend of his youth and also a friend from childhood of the physicist August Kundt, to whom Roentgen ascribes his own success, reveals some of the beautiful qualities of Roentgen's personality. The letter reveals a warm heart, capable of much sympathy and gratitude, and a personality winsome in its modesty where in many men the opposite would have been found. The letter also gives us an intimate glimpse of the present day conditions surrounding men of Roentgen's class in his native land. To translate Dr. Forssell's comment on this: "The few lines of Roentgen's letter in which he touches upon the present conditions allow us a distressing glimpse behind the curtain back of which the tragedy of his native land is being played out to its end. They picture to us the heroic and silent battle now being waged by the men of learning in Germany, a battle not only against poverty, but against that great weight of depression which Germany's situation brings home to them."

The following is a free translation of an excerpt from Roentgen's letter written to Albert in November, 1922: "For the past two and one-half years I have retired from active life and can do but little physical work; to this is added the depressing circumstances under which we Germans now must labor, for not only must we endure poverty (no new experience) but in deep grief our hearts ask what is to be the future of this people, and how shall they ever re-establish themselves? It indeed requires great courage and faith to walk unbowed these days."

"The gay and happy days of our youth, which your letter recalls, are now only a memory, but a memory that awakens music in my old heart. A number of years ago, to my great joy, Besser was my guest (Besser was a friend of student days, later a prosperous business man, but now long dead) and we lived again in memory the years we spent together in Zurich. All three of us have no need to complain of that which life has dealt us, and least of all should I be discontented when I reflect that at that particular time my future appeared very uncertain. Do you remember that it was through you that I was put in touch with Kundt? It was he who guided me through the field of physics

and who led me out of the mist of my uncertainty regarding my future."

Roentgen, says Albert, was a staunch and true friend—a most modest student who never sought to dazzle others by his brilliancy as he might have done. Albert adds that, much as he was liked by the student set, "he had no liking for noisy diversions, dancing, for example."

Such men as Roentgen, concludes Dr. Forssell, are bright stars of hope lighting the way to a better future for their native land, their influence must bear fruit.

It is interesting to note here that the Roentgen Society in England has appointed a committee to consider the setting up of a "Roentgen Award" to commemorate the man to whose research the world is debtor.

Some Remarks on Processus Posterior Tali. Chr. J. Baastrup, M. D., *Acta Radiologica* 2:166-173, No. 6, May, 1923.

THE literature upon fracture of this process is reviewed and the author reports two cases coming under his personal observation and examination.

After this form of fracture there are seen fragments joined to a large and plump bone projection which usually will cause a diminished plantar flexion on account of plantar disproportion. Such a condition of the process may also be congenital. Surgical removal of the process is the only effective treatment.

Whenever there occurs a fracture of the hindmost edge of the tibia the posterior process of the astragalus should be examined for fracture, and vice versa.

X-Ray Diagnosis of Bone Lesions. Robert W. Lovett, M. D., *Illinois M. J.*, 54:48-49, July, 1923.

CHANGES in bone and their relation to clinical phenomena are discussed under atrophic changes, destructive changes and formative changes.

In atrophic changes "where the bone shadow diminishes, the contrast between the cortex and the medulla becomes extremely sharp and in the severer cases the medulla casts little more shadow than the soft parts. This accompanies injury, disuse, and is seen in disease—particularly tuberculosis."

Destructive changes are either general or local, may involve a large area or a small one producing perhaps notched out areas. Tuberculosis most often is responsible for these changes though they may be caused at times by osteomyelitis, syphilis and sometimes by arthritis deformans.

Formative changes increase the outline or density of the bone. Arthritis heads the list, syphilis is more often formative than destructive, osteomyelitis is both formative and destructive as are new growths.

The diagnostician must keep in mind that a lesion may possess the characteristics of two groups and that any lesion may show changes not characteristic, e. g., tuberculosis may be formative. In some cases diagnosis is impossible short of the microscope. However, x-ray plus clinical findings usually suffice for diagnoses.

Stereoscopy of the Accessory Sinuses.
G. W. Grier, M. D. Am. J. Roentgenol. 10:497-500, June, 1923.

STEREOSCOPY of the accessory sinuses is urged as a routine procedure. The practical advantages are so great that a short trial will convince one that he cannot afford to omit the procedure. The technique is described and the author states that it is not difficult nor time consuming. Three minutes suffices for fitting the head to the head rest and for taking two sets of plates. The information yielded by this method is not procurable in any other way.

"The position which the tube shall occupy for the different exposures is determined by laying out the angles on a sheet of paper and then transferring them to a triangular sheet of aluminum with which the actual measuring on the patient is done. Since there is but comparatively little difference in the size of heads, it is practical to make sinus exposures with a fixed distance between the tube target and the plate. The procedure is easier if a small cone is used on the tube stand and the end of the cone brought a short distance from the back of the patient's head. With the tube in this position, the distance from the target to the plate is measured and this distance is used as the altitude in drawing a triangle, base up, which is to determine our angles. The base of this triangle is twice the distance between the pupils of the eyes, or four inches. The triangle so constructed is halved by bisecting the base line. We now have the three angles at which to make our exposures, represented by the sides of the two triangles, and as the middle angle is the stereoscopic distance, or two and one-half inches from either end, it will stereoscope with either.

"This triangle is drawn full size on a piece of paper and the resulting angles are copied on an aluminum triangle which is fixed to the head rest or which may be used by placing it against the side of the patient's head in

the usual way. One side of the aluminum triangle is so placed as to connect the external auditory meatus and the external canthus, the point of the triangle at the canthus, the base of the triangle extending toward the forehead. The altitude of this triangle then roughly outlines the base of the skull. The first exposure, or the one made at the greatest angle, is made at an angle of 30 degrees to the base line. This is easily done by tilting the tube so that a line drawn down lengthwise through the middle of the cone would be continuous with the line drawn on the aluminum triangle. The two succeeding exposures are made at the remaining angles in a similar manner.

"We thus get three good plates, any one of which is a perfectly good flat plate, the middle one stereoscopic with either one of the others, being the plate for the right eye with one and the plate for the left eye with the other. When viewed singly, the plate made at 30 degrees shows the frontals best, and the last one shows the maxillaries best. The middle one is made at about 25 degrees which is the universally accepted angle."

Pneumoperitoneal X-Ray Diagnosis.
H. D. Mitchell, M. D., J. Am. Inst. Homeopathy, 15:705, Feb., 1923.

INTRAPERITONEAL injection of gas does not displace any of the present methods of diagnosis, but is used as an adjuvant to those methods now in vogue. Changes in contour, size, position or adhesions of the liver are most adapted to this procedure. The gall-bladder is often pictured. The spleen and the kidneys show readily, the tail of the pancreas often shows. Adhesions any place in the abdomen are well shown. Retroperitoneal glands or tumors can be shown. The question as to whether masses are above or below the diaphragm is easily answered. The uterus (normal or pathologic) can be shown, also the normal tubes and ovaries (as an indicator of the patency of the tubes it is apparently infallible), adhesions to the sigmoid and new growths which change the conformation of the uterus tubes or ovaries. Pregnancy can be differentiated from fibroids or neoplasms of the ovaries. Acute salpingitis is readily shown.

There are few contra-indications, but patients with definite heart lesions and dyspnea, those with acute diseases, e. g., salpingitis, temperature or status lymphaticus should not be examined by this method.

Carbon dioxide is preferred to oxygen because of its rapid absorption

and consequent early relief of any distress which the inflation has caused.

The organ to be rayed must be surrounded by the gas and the patient must be manipulated to bring this about. The radioscopic technique does not differ from that employed in the examination of the abdomen by other methods, except that the exposures must be less.

The Furniss method for determining the patency of the tubes is advised.

—W. WARNER WATKINS, M. D.

Annular Shadows: Are They Cavities or Spontaneous Pneumothoraces?
Philip King Brown, M. D., Am. J. Roentgenol. 10:445-453, June, 1923.

THE writer believes annular shadows can be proved to be lung cavities and believes that any lighter interpretation of them is a serious matter.

Many hundreds of such cases have been examined by him and while he admits that a localized pneumothorax might show as an annular shadow he has not met any such manifestation.

His reasons for this belief are as follows: (1) Antero-posterior and lateral views show these shadows to be equally round in all directions. (2) Artificial pneumothorax first compresses and then collapses these shadows and moves them from their original positions. (3) Pneumothoraces containing fluid will not empty, cavities will. (4) Stereograms have been taken by the author in 1/60 second, eliminating all motion and giving a detail never before secured in lung plates. These stereograms have shown the perspective of the shadows and their connection with the bronchi and how they increase in size by coalescing with adjacent and often with very small cavities.

If these four tests are applied the author contends that the manifestations will be found to be cavities and adds that in fairness to the patient these tests should be applied.

Diagnosis of Chest Lesions, Non-Tuberculous. A. Z. Ritzman, M. D., Pennsylvania J. Roentgenol. 4:20-25, July, 1923.

FOREIGN bodies opaque to roentgen rays are located by direct signs, those bodies not opaque to the rays are located by indirect signs.

In locating an opaque body if the small diameter is seen in the antero-posterior view the body is in the esophagus, if the large diameter is seen in this view then the body is in the trachea. If localization is still uncertain the patient should be turned partly to the left and a thick barium

mixture given. If the barium column is seen posterior to the foreign body or passing around it localization is complete and a radiograph will show the body in the trachea.

In locating a non-opaque body in the lungs or bronchi there are three characteristic signs to depend upon: (1) increased transparency over the entire affected side; (2) depression of the diaphragm on the affected side; (3) displacement of the heart and mediastinal structures away from the affected side. These signs are best seen at the end of expiration.

The normal pleura is not visible by x-rays and the pleural cavity is seen only when filled with fluid or air or both. The first radiographic symptom of pleurisy with effusion is a fixation of the diaphragm which may be detected before any fluid is seen. The quantity of fluid may vary greatly from a small amount in the costophrenic cavity to an amount sufficient to displace the heart and aorta. A thickened pleura or an unresolved pneumonia may be mistaken for fluid. Serum and pus cannot be differentiated.

Examination for lung abscess should be made with patient in the upright position and should never be made just after a severe paroxysm of coughing as the abscess may then be empty.

Syphilis of the lungs is difficult to diagnose.

X-ray study of the heart has not reached a satisfactory stage. There are a great many factors to consider in this diagnosis and omission of any one of them may lead to a mistaken conclusion.

Pulmonary Tuberculosis as Shown by the X-Rays—Without Physical Signs. Stanley Melville, M. D., *Arch. Radiol. & Electroth.* 28:23-28, June, 1923.

THE author reports four cases of pulmonary tuberculosis, without physical signs, in which diagnosis was established by x-rays.

A recent statement in a book lately published by an eminent clinician and pathologist is to the effect that the x-ray does not detect tuberculosis in the absence of physical signs. This is contrary to the experience of the writer of this paper.

A Study of Lobar Pneumonia and Its Pulmonary Complications by Serial Roentgenographic Examination. L. R. Sante, M. D., *Am. J. Roentgenol.* 10:351-365, May, 1923.

OF the 272 cases of frank lobar pneumonia treated by this author during the last two years 152 were

subjected to roentgenographic examination at three day intervals throughout the course of the disease and these findings were correlated with the clinical history and physical signs. The author's summary reads thus: "(1) Owing to the similarity in appearance, differentiation between the stages of active consolidation in lobar pneumonia is impossible from the roentgenogram. (2) In the majority of cases, lobar pneumonia starts as a consolidation in the hilus region, rapidly spreading peripherally, and involving an entire lobe. In a few cases in children, the onset of consolidation is cortical and progresses toward the hilus. (3) The shadow produced is homogeneous and is usually confined to one or more lobes. (4) During the stage of resolution the shadow becomes mottled and irregular, complete resolution being effected often in a very short time—three days. (5) The average time for resolution is seven to ten days after the crisis. Persistence of the shadow or failure of resolution after fourteen days is distinctly pathological, and suggests some complicating lesion. (6) The pulmonary complications most frequently encountered following pneumonia are: (a) Dry pleurisy, with thickening of the pleura. (b) Pleural effusion, either serous or purulent, and either general or local. (c) Plastic serofibrinous pleurisy. (d) Chronic interstitial pneumonia or fibrosis. (e) Lung abscess. (7) Their roentgenographic differentiation is indicated."

Sixteen illustrations accompany the text.

The X-Ray Picture of Interlobar Exudates and of Induration of the Pleura with Particular Attention to the Differential Diagnosis of Tuberculous Infiltrations in the Upper Right Lobe. P. Flemming-Moeller, M. D., *Acta Radiologica*, 2: 139-155, No. 6, May 1923.

CONTRARY to general opinion, the x-ray examination does not yield absolutely reliable proof upon which to base a diagnosis of interlobular exudate. The exudate gives a characteristic picture but the same picture is seen in pulmonary tuberculosis and in simple bronchopneumonia. Therefore the picture is not conclusive and must be taken in connection with the clinical history and physical findings. A test puncture is the only conclusive evidence.

However, a well defined lower border of shadow is more apt to indicate an infiltration than an exudate, and vice versa. Interlobular induration of the plura is prognostic of eventual pulmonary tuberculosis.

Pulmonic and Cardiac Changes Following Inoculation with Foreign Protein. I. Edward Liss, M. D., *Am. J. Roentgenol.* 10:435-437, June, 1923.

THIS investigation covered 33 cases of which 9 had been inoculated with typhoid vaccine, 16 with diphtheria antitoxin and 8 with influenza vaccine. The larger percentage showed definite pulmonary changes after injection of the foreign protein, a smaller percentage showed cardiac changes.

Investigations Regarding the Condition of the White Blood Corpuscles in Guinea Pigs and Rabbits Exposed to Irradiation with Visible Rays. Carl Sonne, M. D., *Acta Radiologica*, 2:116-127, No. 6, May, 1923.

THIS is a report from the Finsen Medical Light Institute in Copenhagen. It reviews the research along this line by other workers and presents the author's own studies.

His summary follows: "By irradiation of white shaved guinea pigs and rabbits with visible luminous rays a perceptible effect on the condition of the white blood corpuscles is proved. In guinea pigs an immediate decrease in the number both of lymphocytes and leukocytes occurs, but this is most pronounced for the former. Later when the irradiation has ceased, an increase in the number of lymphocytes occurs in the course of a few days, so that this number exceeds the normal for some time. Coincidentally the number of the polynuclear leukocytes seems to be, if anything, normal. These changes correspond to those found by Murphy and Sturm with regard to the temporary influence of dry heat on rats, mice, and guinea pigs.

"In rabbits, forty-five minutes after the irradiation, there is a very considerable increase in the number of polynuclear leukocytes, simultaneously with a generally somewhat smaller decrease in the number of the lymphocytes, so that the normal strongly pronounced lymphocytic form has in the course of two to three hours become leukocytic. Next day the form is again normal, so that it can once more be affected in the same manner by a new light-bath."

The Effects of Roentgen Rays and Radioactive Substances on Living Cells and Tissues. Leo Loeb, M. D., *J. Cancer Research*, 7:229-282, October, 1922.

THIS article treats of the subject under (1) sources of radiant energy within the body; (2) differences in the resistance to radiation of different

tissues in mammals; (3) effect of radiation on nucleus and cytoplasm; (4) effect of radiation on tumor cells; (5) quantitative graded effects of radiation upon tissues and tumors; (6) stimulating effects of radiation; (7) latent period; (8) relation between intensity and character of rays and their effects on cells and tissues; (9) phenomena of immunization after repeated radiation; (10) indirect effects of radiation on resistance and immunity; (11) toxemia after radiation; (12) comparison of the effects of radiating tissues in vitro and in the living organism.

The observations, studies and conclusions of many leading authorities are here discussed and are cemented into a whole by the author's knowledge of the subject. A bibliography of about one hundred articles accompanies the text.

A Critique of Tumor Resistance. William H. Woglom, M. D., J. Cancer Research, 7:283-299, October, 1922.

ORIGINAL observations from experimental study are recounted in this article. The author's conclusions read as follows: "Because the doctrine of resistance has proved so barren and so inconsistent, it is proposed that propagable tumors be investigated from another aspect, and the relation between a tumor and its blood-vessels is suggested as perhaps worthy of consideration.

"The question is raised whether the receding tumor may not differ from the growing one only in the extent to which its blood vessels have been obliterated by thrombosis, and whether every growing tumor may not therefore be potentially a receding one."

The Regression of Spontaneous Mammary Carcinoma in the Mouse. William H. Woglom, M. D., J. Cancer Research, 7:379-394, October, 1922.

ABOUT 2000 mouse tumors furnished the basis for this study. Regression may take place by recession without any appreciable morphological alteration not to be distinguished microscopically from a growing neoplasm, or regression may take place by widespread necrosis, or complete keratinization.

No common histological feature has been found in receding carcinomata. Regression does not seem to be brought about by any constitutional alteration in the bearer as far as these studies show.

"The factor responsible for spon-

taneous cure appears to reside neither in the stroma nor in the parenchyma of the tumor though the latter cannot be entirely eliminated. By exclusion only the blood vessels remain, but it cannot be shown from the material here discussed that vascular changes underlie spontaneous cure."

The Present Cancer Problem in the United States. Frederick L. Hoffman, LL. D., Consulting Statistician, Prudential Insurance Company of America. The World's Health (Red Cross) 4:18, May, 1923.

THE writer states that the death rate from cancer in the continental United States is probably 90 per 100,000 and the annual mortality from cancer not much less than 100,000. This is an increase of 25,000 since the educational campaign against the disease was organized. This education, nevertheless, he believes will greatly aid in the control of cancer.

The true status of facts is at present largely a matter of conjecture as statistics are not properly kept and sometimes not kept at all.

Alleged cancer cures are gaining in popularity because many of them at first give relief. The disastrous results which follow call for an investigation of the whole subject of alleged cancer cures.

The rarity of cancer among pure native tribes the writer believes offers a field of study to investigators and might shed some light upon the cancer problem. The negative aspects of cancer study he believes have received too little attention.

Intrathoracic Changes Following Roentgen Treatment of Breast Carcinoma. T. A. Groover, M. D., A. C. Christie, M. D., and E. A. Merritt, M. D., Am. J. Roentgenol. 10:470-476, June, 1923.

THE authors believe that large doses of roentgen rays delivered to the deep structures by means of prolonged treatment through a copper filter bring about changes in the pleura and often in the lungs. These changes are analogous to those produced in the skin and the symptoms of intrathoracic irritation closely follow the course of the skin reaction.

Observations are based upon clinical and roentgen findings and are not offered as definite proof that the rays are responsible, but that is the author's belief.

Breast Carcinoma Treated Surgically and by Roentgen Ray. Cassie B. Rose, M. D., J. A. M. A. 80:1750-54, June 16, 1923.

THE two cases here reported with clinical and postmortem findings, are submitted as contributions to the study of roentgen ray therapy. Similar cases have been presented by others but without necropsy reports.

The clinical pictures were much the same in each, both were carcinomas of the breast, the first case had had three operations, the last one was followed by roentgen ray treatment. The second case had had two operations, the last one followed by palliative roentgen ray treatment.

Postmortem of the first case showed a large pleural effusion without pleural thickening in the right chest at the site of the tumor and where the greatest amount of x-ray had been received, but no carcinoma was present. No inflammatory process of the pleura was present but there were two small tuberculous foci in the apex of the right lung. The writer believes that the rays lowered the patient's resistance to tuberculosis and stimulated the effusion.

The second case, upon postmortem, showed pleural thickenings and a large pleural effusion of the left side of the chest (site of the second tumor and of greatest amount of roentgen ray treatment) which may have been accounted for by the numerous carcinomatous nodules found in the pleura. Central necrosis in the small nodules "speaks strongly for the destructive action of roentgen rays on carcinoma cells" * * * abundant stroma surrounding the tumor nodules, and the marked fibrous thickening of the pleura, speak for the stimulation of fibrous tissue by the roentgen rays * * *

Pernicious Aplastic Anemia. Knud Faber, M. D., Acta Radiologica, 2:110-115, No. 6, May, 1923.

THIS is a case report from the medical clinic of the University of Copenhagen and it reports the case of Dr. Nordentoft who after many years practice in radiology fell a victim to pernicious aplastic anemia.

The first symptoms were noticed many years ago but did not become very alarming until the latter part of 1921. Arsenic and iron, also intravenous injections or protein, were used but without success.

A similar kind of anemia has been observed in two other radiologists and in three x-ray technicians and the writer does not doubt that it was caused by the effect of the hard rays.